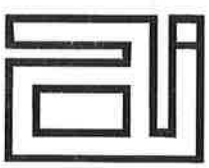
Adverse effects of organic solvents on fertility and reproduction; a critical review

Conducted at the request of the Directorate General of Labour by:
the TNO-CIVO Toxicology and Nutrition Institute;
in cooperation with:
the Coronel Laboratory of Occupational and Environmental Health,
Faculty of Medicine, University of Amsterdam

Directoraat-Generaal van de Arbeid



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ADVERSE EFFECTS OF ORGANIC SOLVENTS ON FERTILITY AND REPRODUCTION A CRITICAL REVIEW

1. INTRODUCTION

1.1 Physico-chemical properties and usage

Organic solvents are volatile lipophilic liquids, which are able to dissolve lipids and high-molecular weight compounds. They are widely applied in many occupational activities and also sometimes at home. Solvents may also be used in chemical synthesis and as plastics monomers, as fuels, anaesthetics, addictive drugs and as solvents of pharmaceutical drugs and cosmetics.
In this review styrene and carbon disulfide are not discussed, because they are not mainly applied as solvents. Both agents will be reviewed elsewhere. Ethyleneglycol, formamid and dimethylformamid have been reviewed and are reported in separate annexes.

1.2 Combined exposure

Usually workers are not exposed to a single solvent. Exposure to tetrachloroethene in dry cleaning shops may be one of the exceptions, although exposure to contaminants may also exist. Moreover, there also is exposure to the chemicals that are being dissolved, e.g. in paints and glues. The principal way of exposure is by inhalation of vapour, although many solvents - being lipophilic - may also penetrate the skin. In the case of a few solvents the latter route is even considerable. Exposure should be assessed where possible by means of biological monitoring of exhaled air, blood and/or urine.

1.3 Classification

Solvents may be classified into a number of categories. The most important are:
- aliphatic hydrocarbons (HC), e.g. pentane, hexane
- alicyclic HC's, e.g. cyclohexane, cyclohexanone
- aromatic HC's, e.g. benzene, toluene, xylene

- no positive confounder was available (i.e. a factor which was predictive of the occurrence of the endpoint and was associated with the exposure being investigated)
- the association was strong (e.g. RR>2) or, if not strong, it was substantiated in two or more studies
- the results were unlikely to be due to chance alone (i.e. the statistical power of the study seemed to be sufficient as to detect the reported association) or
- several independent studies done under different circumstances made the cause-effect relationship more likely or, alternatively, several case reports showed association between a very rare exposure and a very rare endpoint.

Limited evidence was achieved when several case reports or uncontrolled chemical series were available and biases, when present, were unlikely to explain all of the reported association, and the association was weak and not shown to be reproducible.

Low level of evidence was based on the following: few case reports or clinical studies, geographic and/or chronological correlation studies only, individual analytical studies showing a weak and biased and/or a confounded association.

Inadequate evidence was based on studies showing serious bias or serious confounding or on insufficiently available information.
It should be understood that this classification only reflects the qualitative levels of available knowledge; it does not indicate a different potency of chemicals

2. REVIEW OF HUMAN DATA

2.1 Risk of exposure of female with respect to reproductive organs, the endocrine system and fertility

2.1.1 Gynaecological disorders

Zielhuis et al (1984) discussed six studies (published in 1944 to 1978) with evidence of disturbed menstruation; the data have been summarize in Table 1a. Some other studies, which are not discussed by Zielhuis et al (1984) are summarized in Table 1b.

Of the ten studies summarized in Tables 1a and 1b nine suggested menstrual disorders; several also mentioned other gynaecological disorders. In most studies there was exposure to aromatic hydrocarbon solvents in addition to other solvents and non solvent-chemicals. Generally the quality of the data on exposure, epidemiologic design and methods was poor. On the other hand, almost all studies indicated a trend of an increased risk of menstrual disorders and in several studies also of other gynaecological disorders. The overall evidence for an increased risk of menstrual disorders can be considered "limited". With respect to other gynaecological disorders the evidence should be considered "low level".

2.1.2 Effects on the endocrine system

In their review of East-European literature Izmerow et al (1978) mentioned that the absence of changes in vaginal cells in female workers exposed to aliphatic HC's (benzin) and dimethyldioxane in rubber (tire) workers, as indirect evidence of absence of disturbed ovary function, although disturbed menstruation was observed (see Table 1a). Takeuchi et al (1972, Japan) described two cases of diencephalon syndrome (hypofunction of the diencephalo-hypophysio-adrenal cortex system) in workers of a factory producing paints and lacquers. To date the occurrence of endocrinological effects in exposure to solvents has hardly been studied yet. The evidence is regarded to be "inadequate".

2.1.3 Fertility

Heidam (1983, Denmark) studied the fertility of 262 female factory workers exposed to solvents and of 241 female non-exposed shop assistants and packers,

all working during at least one pregnancy period. Fertility was defined as the number of infants given birth to in 1972-1980. There was no evidence of a decreased fertility in the factory workers; they even had a slightly higher fertility: respectively an average of 1.53 and 1.49 children born per woman. The data indicated a significantly stronger tendency ($p=0.01$) to continue childbearing among these factory workers, regardless the outcome (abortion or surviving children) of previous pregnancies. The method of assessment of fertility was not the most appropriate one; a better method might have been to count apart from the number of pregnancies also the time between the decision of not using anticonceptives and first week of pregnancy. Moreover, no data were presented on induced abortion and anticonceptive measures. Barlow and Sullivan (1982) quoted the study by Mukhamatova and Vozovaya (1972, USSR): no effect on fertility was observed.

Rachootin and Olsen (1983, Denmark, see also 2.4.2) studied in a case-control study couples who were examined or treated for infertility at Odense University Hospital during 1977-1980. In a study of 94 subfecund cases and 2969 fecund controls the Odd's Ratio (with 95 % confidence limits) for women exposed to degreasers was 1.2 (0.6-2.6), for lacquers, paints, glues 1.4 (0.8-2.6), for other organic solvents 1.6 (0.7-3.3), for dry cleaning chemicals (tetrachloroethene?) 3.0 (1.2-7.4; after correction for age, education, residence and parity 2.7 (1.0-7.1)). Women working in dry cleaning shops (tetrachloroethene?) showed a significantly ($P<0.05$) increased Odd's Ratio in those with idiopathic infertility with evidence of hormonal disturbance and in those with delayed conception. The authors, however, emphasized some possibilities of information bias and confounding and they questioned the validity of the occupation-exposure linkage. The evidence of an increased risk of infertility is "inadequate".

2.1.4 Cancer of reproductive organs and breast

Blair et al (1979, USA), suggested an increased risk of cervix cancer deaths (Proportional Mortality Rate, PMR) in female laundry and dry cleaning workers in Missouri exposed to tetrachloroethene; however, subsequently Katz and Jowett (1981, USA) examined the cervical cancer deaths (also PMR) of a larger group of female dry cleaning workers in Wisconsin; the increased rate disappeared after correction for the socio-economic status (SES).

Duh and Asal (1984, USA) examined the mortality experience of 440 laundry and dry cleaning workers during 1975-1981 in Oklahoma. The dry cleaning solvents currently in use in the dry cleaning industry can be classified as "synthetic" and "petroleum" solvents; the first group includes tetrachloroethene (PER) and trichlorotrifluoroethane (fluorocarbon 113). About 75 % of commercial dry cleaning establishments in the USA used tetrachloroethene (PER). The second group comprises stoddard solvents and 140F solvent, both of which resemble gasoline (benzin), i.e mainly aliphatic HC's. However, in Oklahoma the use of the second group accounted for more than 50 % of the total amount of solvents used, in contrast to the overall USA. The mortality of laundry and dry cleaning workers was compared with that in the State of Oklahoma; the data of the laundry workers (no exposure to solvents?) could not be separated from those of the dry cleaning workers, which may have led to an underestimation of risk. Both male and female workers were included, in contrast to the study of Katz and Jowett (1981). No correction was made for the SES. Deaths due to breast cancer were significantly decreased (Stand. Mortality Odds Ratio 0.1, 95 % confidence interval 0.0-0.4). On the other hand, deaths due to corpus uteri cancer were not increased, as well as that due to cervix and ovary cancer. According to the authors the deficit of breast cancer mortality might reflect the rather low SES of the workers, because of the well established inverse relationship with SES.
The overall evidence should be regarded as inadequate.

2.2 Risk of exposure of females with respect to pregnancy and prenatal development

Solvents may be transferred to the fetus by transplacental passage. In addition, already prior to the development of the placenta the embryo may be exposed to solvents. Laham (1970, USA), examined the trichloroethene levels in maternal and fetal blood at delivery under trichloroethene and nitrous oxide anaesthesia in deliveries; the mean ratio was 1 at about 10-20 min exposure. In three cases the fetal levels were higher than the maternal levels. A similar study was carried out by Dowty et al (1976, USA) in 11 paired samples of maternal and fetal blood at delivery. All infants were normal, except one with a lumbosacral meningomyelocele; all were of normal weight. Many volatile low molecular weight compounds, including halogenated hydrocarbons, plastic

components and food preservatives were detected in maternal and cord blood. Benzene, carbon tetrachloride and chloroform were present in cord blood in concentrations equal to or higher than were present in maternal blood.

2.2.1 Spontaneous abortion

In table 2a five studies published before 1980 are summarized.
Of the five studies four provide some evidence of an increased risk of spontaneous abortion. However, for all studies essential information on methods and designs is lacking.
The studies reported from 1980 onwards will be discussed in more detail.
Nizyaeva (1982, USSR) studied the effects of exposure to acetone on reproduction in an acetate-fiber production and textile plant. In the fiber production department the levels of acetone in the workroom air were about 300 mg/m^3, with 30 % of the samples above 600 mg/m^3 (Max. Perm. Conc. 200 mg/m^3); in the textile section most levels were below 200 mg/m^3, 20 % less than 400 mg/m^3; in the production department of chlorinated fibers only 17 % exceeded 600 mg/m^3, most levels were less than 400 mg/m^3; in the textile section all levels were below 200 mg/m^3. The total number of exposed female workers and of controls was not presented.
In 20 to 50 % of the workers and in 10 to 40 % of various control groups the following most important pregnancy complications occurred: impendent abortion ($p<0.001$), toxicosis during the second half of pregnancy ($p<0.02$), weak uterus contractions during labour ($p<0.01$). There was an increasing duration of exposure.
The author considered the effects on reproduction as secondary to a decreased functional state of health of the mother (acidosis, disturbed carbonhydrate and fat metabolism, neuroendocrine dysregulation). However, the presentation of the data was poor: no adequate information on number of exposed workers; no adjustment for age and parity.

Hemminki et al (1984, Finland) published a nation-wide study, based upon information from the Register of the Union of Chemical Workers and the Hospital Discharge Register, supplemented with spontaneous abortions treated in the policlinics. Among laundry workers (probably including dry cleaning establishments with exposure to tetrachloroethene; no data on exposure presented) the data of spontaneous abortion in those exposed during pregnancy

were: n=21; rate (per 100 pregnancies) =7,5; ratio (per 100 births) =11,4; for all Union members: n=149; rate=9.0 ratio=14.0. For those exposed before or after pregnancy: for those working in laundries: n=21; rate=8.6 ratio=11.4 for all union workers, n=110. No evidence of an increased risk of abortion in female laundry workers was observed. Should the groups of laundry workers have comprised many females who were not exposed to solvents, then the risk of exposure to solvents may have been underestimated.

Heidam (1984a, Denmark) carried out a retrospective cohort study of women living in the Funen county. A group of factory workers (A, n=1431) exposed to (unspecified) solvents (and other compounds) in rubber-, machines- and tinindustries, and a group of painters (B, n=81) exposed to solvents (and other compounds) were compared with shopassistants from supermarkets and packers from a warehouse for vegetables (C, n=1034), considered to be of similar socio-economic status. Barring exposure to the chemicals, group A had similar working conditions as group C, but group B had probably difficult working postures than group A and C. Information was gained through a postal questionnaire in 1980 and from hospital records. The response rate was: 85 % for A, 94 % for B and 80 % for C.
From the 357 pregnant respondents A 105 and the 38 pregnant respondents B 35 reported to be exposed to solvents. The OR for those exposed to solvents was 0.7 (95 % C1 0,3-1,5; n.s.) for group A; for B no OR could be calculated because no spontaneous abortion occurred among the three women not exposed. When only the hospital registered spontaneous abortions were taken into account, the age-adjusted OR for A was 1,3 (0,9-1,9) and for B 1,1 (0,4-2,9). Exposure to other chemicals also existed particularly in the factory workers; this may have distorted the comparison. No definite conclusion could be drawn on the risk of spontaneous abortion.

Heidam (1984b; Denmark, Funen county) also carried out another study with a similar design as the above mentioned study among female laboratory personnel (hospital, university, local government and industry) (N=881). They were exposed to various chemicals, including organic solvents. A control group less exposed to chemicals included office workers, technical assistants, designers, physiotherapists and occupational therapists (N=1571). The response rates of the various subgroups were 89 to 97 %. The adjusted OR's for laboratory

workers exposed to organic solvents during pregnancy (N=465) when compared with non-exposed laboratory workers (N=843) were as follows:

	exposure	number of pregnancies	number of spontaneous abortions	percentage	adjusted* OR (95 % CI)
exposure to organic solvents	yes	299	20	7	0.7 (0.3-1.4)
	no	166	18	10	
exposure to other compounds or naphtha	yes	12	0	0	0 (0.0-5.6)
	no	453	38	9	

* for gravidity, pregnancy order and age

The OR's were not increased when exposure to other non-specified chemicals was also considered. However, no data on combined exposure to organic solvents and the other chemicals were presented. The rate of induced abortion among hospital and industrial laboratory workers (respectively 7.9 % and 8.5 %) was slightly lower than the rate for the controls (9.5 %); this suggests that the OR's might be slightly underestimated. This study did not indicate an increased risk of spontaneous abortion after exposure to solvents during pregnancy.

Axelsson et al (1984, Sweden) conducted a retrospective cohort study of a group of female employees of the university of Gothenburg laboratories. A comparison was made between the outcome of pregnancies while exposed to solvents during pregnancy and while not-exposed. The group comprised of 782 women born in 1935 and thereafter engaged in laboratory work between 1968 and 1979. The questionnaire data were verified through the Medical Birth Register; only those verified were included in the analysis. Information on non-respondents (5 %) was gathered from the Register and hospital records. Adjustment took place for various other potential causes of abortion

(infectious disease, use of medicines, work in the radiological department, heavy physical work, stress) and also for parity, age, year of pregnancy, previous miscarriage and shift work (because of an increased abortion rate in shiftwork these pregnancies were not included in the final analysis). Of the 745 respondents 556 reported to have been pregnant; the non-respondents had a higher abortion rate (15,7 %) than the respondents (10,8 %; n.s.). The rate was not higher when laboratory work was performed than when pregnant under other conditions off work. Parity, age and shiftwork were significantly negatively related with working with solvents. Exposure to solvents in the first semester was not associated with a significantly increased relative risk: RR=1,31 (0,89-1,91) after adjustment for parity, age and shift work. There was also no association with the frequency of exposure ("sometimes" to "daily"). The miscarriage rate was calculated in relation to exposure to 14 solvents separately: chloroform, methylenechloride, toluene, acetone, xylene, ether, benzene, methanol, ethanol, propyleneoxide, dichloroethane, phenol, petroleumether and "other solvents". Those who reported exposure to petroleumether had an increased abortion rate of 28.6 % (observed 6, expected 2,04; $p<0.02$; small numbers). However, in a large series of computations of p, one might have found a significant p by chance. The exposure data were usually only qualitative. The authors concluded that the abortion rate did not appear to be increased, but this result "could not be used to disregard laboratory work as a risk factor". They stressed the importance of verification of questionnaire date by means of hospital records; when the questionnaire data had been analyzed without verification, then there would have been a significantly increased RR of 1.43 (1.02-2.00).

Lindbohm et al (1984, Finland) carried out a nationwide retro- and prospective mixed cohort/case-control study over 1973-1976. A variety of exposures was studied, among which women exposed to solvents (graphic workers, painters, rubber and plastic workers, laundry workers); all other economically active women served as reference group. Information on maternal and paternal occupations, number of children and their dates of birth and women's level of education was obtained from the 1975 National Census. Data on reproduction could be collected for 92 % from the Hospital Discharge Register. The total material comprised 2943 pregnancies.

Analysis of spontaneous abortions for each exposure group was performed on the pregnancies occurring in 1976 (prospective); occupational exposures referred

to the end of 1975. The association with specified occupations was based upon the data on reproduction over 1973-1976 (retro-and prospective). The effects of exposure on the abortion rate was adjusted by linear logic regression for age, parity, marital status, place of residence (Helsinki versus other districts).
The adjusted relative risks of spontaneous abortion amongst women and their husbands exposed to solvents were in 1976 as follows:

N-pregnancies	Odd's Ratio	95 % CI
women exposed		
730	0.79	0.58-1.07
husbands exposed		
1316	0.86	0.69-1.08

The data for spontaneous abortion in specified occupations of women with exposure to solvents (laundry workers) was: N-pregnancies=416, adjusted OR=1.48 (95 % CI=1.09-2.02, p>0.01). There were no specified paternal occupations with exposure to solvents which revealed any increased risk; neither was this the case for male laboratory workers (see 2.5.1).
The exposure data were based upon registered occupational titles and not on personal questionnaire data, let alone on quantitative data. The heterogenicity of the intensity of exposure may have diluted possible effects and may so have underestimated the actual risks, also in the laundry workers. Because of the negative relation between smoking, drinking habits and morbidity with social-economic status, these factors may at least have been partly adjusted for. Because the data were adjusted for age, parity, marital status and place of residence, all of which correlate with induced abortion, confounding by induced abortion will have been reduced.
In those assumed to have been exposed to solvents, only those in laundries with probable exposure to tetrachloroethene had an increased risk.

Exposure in the graphic industry as painters, rubber or plastic workers, also with potential exposure to solvents, showed no evidence of any increased risk.

McDonald and McDonald (1986, Canada) studied the rate of spontaneous abortion in about 400 women employed in the leather industry. There was no increased

risk of spontaneous abortion. Exposure existed to glues and paints and therefore also to non-specified solvents (see also 2.2.2 and 2.2.3).

Taskinen et al (1986, Finland) carried out a register-based study on spontaneous abortion among female workers in eight pharmaceutical industries in 1973 to 1980. In 1975 pregnancies the abortion rate during employment was 10.9%, and almost similar (10.6%) for the period before or after employment. In a case-control study of 44 cases of spontaneous abortion during employment in women exposed for at least one week during the first trimester, they were compared to three age-matched pharmaceutical factory workers, who had given birth to a child during employment. Information on exposure was based on a questionnaire completed by the occupational health staff. For methylene chloride (the Odd's Ratio (OR) was of borderline significance (OR=2.3, p=0.06). The OR was significantly increased among those exposed to four or more solvents (OR=3.5, p=0.05) and higher than among those exposed to one to three solvents (OR=0.8, p=0.74). The workers might have been exposed to the following solvents in their main tasks (frequent exposure): aliphatic solvents, alicyclic solvents, toluene, xylene, benzene, chloroform, methylene-chloride and "other solvents". The authors considered that this study supports the view that organic solvents, and methylene chloride in particular, may have harmful effects on the pregnancy. Particularly the frequency of exposure and the exposure-response relationship add to the credibility of a causal relationship, although confirmation by an independent study is needed.

General discussion and conclusions

This review discussed 13 studies. Table 2a summarized 5 older studies, generally of poor quality; in table 2b the 8 more recent studies are summarized, generally of higher quality. Of this last group only the four studies by Nizyaneva (1982), Axelsson et al (1984, maybe only with respect to exposure to petroleum ether), Lindbohm et al (1984, only in laundry workers) and Taskinen et al (1986; suggestive evidence of an increased risk in exposure to methylene chloride, and probably to four or more organic solvents) presented some evidence of an increased risk.

From these four studies three are from Scandinavian countries; it may be expected that the exposure levels at work in these countries are rather low in

comparison to other countries with a lower level of occupational hygiene. Therefore, these studies may underestimate the actual risk of solvent exposure. The overall evidence is considered to be of "low level" quality.

2.2.2 Congenital malformations

Schardein (1985) quoted some case reports. An infant with Aicard's syndrome was born to a woman who had worked in a paint factory (exposure to organic solvents and other chemicals) during the first 8 weeks of pregnancy (Rin et al, 1982, Japan). Hunter et al (1979) described two cases with hypertonia, scaphocephaly and other abnormalities, of whom the mothers had excessive exposure ("sniffing") to gasoline during pregnancy ("fetal gasoline syndrome"). Euler (1967) reported two infants with multiple malformations born to women working in a shoe factory with exposure to trichloro-ethene and toluene. Toutant and Lippman (1979) described an infant with malformations (micro-cephaly, peculiar facies, similar to that of the "fetal alcohol syndrome"), born to an alcoholic woman who was also addicted to solvents, primarily toluene.

Kucera (1968; Czechoslovakia) examined the incidence of congenital abnormalities of the spine in 1959-1966 (1.500.000 births, number of congenital abnormalities 20.000). In 5 of 9 cases of skeletal defects the mothers had been exposed to solvents during pregnancy. Schardein (1985) quoted a case study by Kucera and Benazova (1962, Czechoslovaka) of a camptomelic syndrome in an infant of a mother with close contact with acetone and other chemicals during the 5th - 8th week of her pregnancy.

Hers et al (1985, USA) recently described three cases of infants with micro-cephaly, central nervous system dysfunction, minor craniofacial limb anomalies and various growth deficiencies, who were born to women inhaling large quantities of pure toluene ("sniffing") during pregnancy. There were similarities with malformations following in utero exposure to alcohol, certain anticonvulsants and hyperphenylalaninemia; the authors considered this to be a non-specific teratogenic phenotype characterized by alterations in growth, development and morphogenesis.

Syrovadko and Malysheva (1977, USSR, only as summary available, see also 2.1) studied 190 women engaged in the production of enamel-insulated wire; they were exposed to chlorobenzene (11-429 mg/m³), ethyleneglycolmonoethylether, tricresol (0.8-18.7 mg/m³) and solvent naphtha. In 150 controls the incidence of congenital anomalies (mainly congenital heart defects and clubfoot) was 3.9%, in those exposed 10.0%. The sufficient details on methods and design are available to assess the validity.

Holmberg (1979) and Holmberg and Nurminen (1980) performed in a nation-wide study in Finland with a case-control design the relationship between the occurrence of congenital abnormalities of the central nervous system (CNS) and occupational exposure to solvents of the mother during pregnancy. The study was based upon the Finnish Register of Congenital Malformations (1-1-1976 to 31-5-1978). All mothers were personally interviewed inter alia on mother's occupation and whether she had remained at work during pregnancy as well as on the father's occupation. Some estimates of the quality and quantity of exposure were made. Referents were mothers with a delivery immediately preceding the case in the same maternity welfare district.
The total number of cases studied was 99 (anencephaly 40, hydrocephaly 24, spina bifida 16, others 19); in addition 21 cases had more than one CNS-defect; some cases also had anomalies other than CNS anomalies. Of the case mothers 78 had continued working; there was neither difference in this respect with the referents, nor a difference in socio-economic status. Of the case mothers, 12 appeared to have been exposed significantly more frequently to solvents during the first trimester of pregnancy compared to the 3 of the referents (X^2=6.23; $p<0.05$; rate ratio estimate RR=5.5). No difference was observed with regard to exposure to metals, pesticides, dyes, noise, low and/or high temperature working environment or non-ionizing radiation. On the other hand, there was significantly more exposure to various dusts (often textile and cleaning dusts; RR=3.4, $p<0.01$), although the numbers were small (1/17 and 5/45 respectively). Smoking during pregnancy did occur among the case-mothers more frequently than among the referents (RR=2.1; p<005). The conclusions were as follows: (1) exposure to organic solvents during the first trimester of pregnancy might be regarded as a risk factor; (2) solvent exposure and smoking habits varied together; (3) an observed association

between smoking and occurrence of malformations was due to confounding when considered simultaneously with solvent exposure. No specified solvents could be pinpointed.

Holmberg et al (1982, Finland) subsequently carried out a cumulative case-control study on the relationship between the occurrence of orofacial cleft and domestic and/or occupational exposure to solvents in the first trimester of pregnancy: 378 cases (1-1-1977 - 31-5-1980) from the nation-wide Register of Congenital Abnormalities were studied. As a reference group those births preceding the birth of the cases in the same district were chosen. All 378 case and referent mothers received a questionnaire requesting information on the intake of drugs, smoking and drinking habits. The interviewers had no knowledge of the study objective. The interviews were validated (Holmberg and Kurppa, 1982): two industrial hygienists assessed blindly the exposure data during the first trimester (only accepted if 1/3 of the TLV was estimated to be exceeded or the estimated peak exposure exceeded the TLV); the information was verified if necessary through personal contact and work visits. Of the case mothers, 14 appeared to have been exposed to one or more of the following solvents: lacquer petrol (85% aliphatic, 15% aromatic HC's), xylene, toluene, ethylacetate, alcohol, methylethylketone, acetone, butanol, styrene, methylenechloride, aromatic solvent naphtha; 4 referent mothers had been exposed to fluorotrichloromethane, petroleumether, benzene (styrene), acetone, lacquer petrol. No specific solvents were predominant. The difference in exposure to solvents between cases and referents was significant (X^2 4.50; $p<0.05$; McNemar test with Yate's correction). Of the cases 9 had also cleft palates (one with additional malformations), 5 only cleft lip. Of the case mothers 8 were exposed at work and 6 at home during the first trimester, in which case fusion of the facial prominences took place. Between case and referent mothers no significant differences existed in parity, age, number of stillbirths or children with other malformations, smoking habits, intake of drugs. No data on alcohol consumption were presented. The authors considered that there existed suggestive evidence of an increased risk of orofacial clefts when the mothers were exposed to solvents during the first trimester.

The same study group (Kurppa et al, 1983, Finland) subsequently carried out another study of 1047 case-referent pairs: 289 defects of the CNS, 421 orofacial clefts, 200 selected skeletal malformations and 137 selected cardiovascular defects in relation to occupational and domestic exposure to

solvents ("selected" means: well definable, visible at birth). The assessment of personal factors and of exposure was similar to that in the previous study. The findings of the previously discussed studies on a relationship between exposure to solvents and congenital malformations of the CNS (first two years: 14/3) were not confirmed in the study over the following three years-period (6/6). This discrepancy might be explained by chance or by the possibility that exposure of the pregnant workers had considerably decreased in the second half of the 70's.

The preliminary results of the total analysis of 1047 pairs pf case-referents were as follows:

	exposure to solvents		total number of defects	p*
	case	referent		
CNS-defects	20	9	289	<0.05
oral clefts	15	5	421	<0.05
skeletal defects	5	3	200	n.s.
cardiovascular defects	3	3	137	n.s.
total	43	20		

* as calculated by the rapporteurs

Further analysis of this data is still going on.
The findings reported by Holmberg et al (1982) on oral clefts were confirmed. There was no evidence of any relationship between exposure to solvents and skeletal or cardiovascular effects. Since the authors selected only those malformations considered to have the most reliable diagnosis and notification, the study did not permit any conclusion on minor defects ad on adverse outcomes related to possible dysmorphogenesis.

In studies on the relation between work in laboratories and in the chemical industry (exposure to many chemicals, inter alia solvents) it is even more difficult to indicate the causal role of exposure to solvents).

Erickson et al (1978, USA) observed that among 989 interviewed mothers 74 of them had babies showing omphalocele or gastroschizis. The frequency of printing craftsmen (potential exposure to non-specified solvents) was 37 times the frequency among mothers of babies with other defects. No healthy controls were studied which makes this study little informative.

Blomqvist et al (1981, Sweden) analysed the pregnancy outcome of women working in the pulp and paper industry. In a subgroup of 162 laboratory workers, 6 cases of major malformation (various types, e.g. cleft palate, anencephaly, cardiac defects) were observed against 2.9 expected ($p=0.07$). Several women were exposed to dyes, ethylacetate and glues; the authors considered that this study itself only provided limited evidence of an increased risk of congenital abnormalities in exposure to solvents, although it supported the evidence of other studies.

Axelsson et al (1984, Sweden, see also 2.2.1) studied the pregnancy outcome of the personnel of a Göthenburg university laboratory, exposed to solvents in the first trimester. 18 Children with malformations of 492 exposed mothers (3.7%) and 21 cases of 496 non-exposed mothers (4.2%) were found, which means no evidence of any increased risk.

Ericson et al (1984, Sweden) identified 1161 infants born in 1976 to women who stated that they had worked in laboratories in November 1975 (national census). The number of all deliveries recorded was 98.354. The number of observed/expected serious malformations were 28/19.1; $X^2=4.1$; n.s. Within the total cohort a case-control study was carried out. Cases of infants who died before the 7th day, and surviving singleton infants with a serious malformation detectable at birth were matched to two controls selected from

infants born to laboratory workers; a total of 26 cases and 50 controls were studied. Exposure to solvents occurred in 9 case-mothers and 16 referent-mothers; the average number of organic solvents was 1.3, both for mothers of cases and controls. The solvents mentioned were: acetone, chloroform, xylene, toluene, benzene, styrene, trichloroethene, vinylchloride. There was no overrepresentation of specific solvents among the cases. No increased risk by exposure to solvents was observed. The questionnaire was not verified by personal contact; smoking and drinking habits were not known. The authors emphasized that an unknown specific exposure might have occurred in both cases and controls; another possibility was that the total multiple and complex chemical exposures influenced the prevalence in both groups, at least in some laboratories.

Hemminki et al (1984, Finland, see also 2.2.1) did not observe any increased prevalence of malformation in women working in laundries (exposure to tetrachloroethene): RR=1.0; 95% CI=0.1-18.9.

Clarke and Mason (1985, UK) carried out a study of perinatal mortality in 1876-1982 in Leicestershire (7500 infants); 1187 infants were stillborn or died within the first week; 56% of the mothers were employed outside their home, which was close to the level for married women in Britain in 1976-1981. Women who were classified as leather workers (shoemakers/-repairers; cutters, sewers and related workers, leather product workers) appeared to have an excess risk of 2.0 (95% CI 1.1-3.6). Only among those categorized as class III among the leather workers (n=over 1000) the RR slightly increased to 2.1 (1.1-4.1). Perinatal death was mainly due to either congenital malformations or macerated stillbirths, which accounted for the excess risk, when compared to other class III workers. The congenital malformations (n=12; 1.1-3.1) included three chromosomal aberrations of the rather uncommon trisomy of Edwards (observed one in 400 births, expected one in 5000 to 7000 births). The women worked preponderantly in closed rooms, with exposure to glues and solvents (ethylacetate). No quantitative data on exposure were presented.

McDonald and McDonald (1986, Canada) studied the pregnancy outcome of about 400 female leather workers (see also 2.2.1); they did not find convincing evidence of an increased risk of congenital malformations.

Discussion and conclusions

The studies reviewed can be summarized as follows (case-reports ommitted):

author year of publication	country	assessment of exposure	type of malformation	comments
Syrovadko and Malysheva (1977)	USSR	semi-quantitative	mainly cong. heart defects and clubfoot	enamel-wire production few details, only indication of increased risk
Holmberg and Nurminen (1979,1980)	Finland	qualitative	CNS defects	nationwide; RR 5.5; $p<0.05$; exposure to dust RR 3.4; $p<0.01$; see Kurppa et al(1983)
Holmberg et al (1982)	Finland	semi-quantitative	orofacial cleft	nationwide X 4.50; $p<0.05$
Kurppa et al (1983)	Finland	semi-quantitative	CNS defects not confirmed; orofacial cleft	nationwide probably significantly increased ($p<0.05$); study still going on
Erickson et al (1978)	USA	qualitative	omphalocele, gastroschizis	printing plants; no controls; only indicative

author year of publication	country	assessment of exposure	type of malformation	comments
Blomqvist et al (1981)	Sweden	qualitative	various malformations	laboratory work; 6 observed, 2.9 expected; p=0.07; weakly suggestive
Axelson et al (1984)	Sweden	qualitative	various malformations	laboratory work; no increased risk
Ericson et al (1984)	Sweden	qualitative	various malformations	laboratory work, no increased risk
Hemminki et al (1984)	Finland	qualitative	various malformations	laundry work; no increased risk
Clarke and Mason (1985)	U.K.	qualitative	various malformations	excess of trisomy; ethylacetate?
McDonald and McDonald (1986)	Canada	qualitative	various malformations	no increased risk; leather workers

The large majority of reasonably designed recent studies have been carried out in Scandinavian countries (including Finland); the data on exposure to solvents generally are presented in more detail than in the older reports. Three studies represent subsequent phases of an ongoing nationwide Finnish study. At first an increased risk of CNS-defects was observed; however, this was not confirmed in a subsequent follow-up period, maybe due to decreased exposure to solvents.
The risk of CNS-anomalies may occur under relatively high exposure conditions to solvents; the evidence is considered to be "low level".

There appeared to be an increased risk of orofacial cleft at exposure to levels below the Finnish and the Dutch MAC-values. Further studies are needed for confirmation; in other small-scale studies such an increased risk has not been demonstrated. The present evidence can be regarded as limited.
Some studies have been carried out in laboratory workers; two were negative, four suggested an increased risk of malformations of the gastrointestinal tract. For the reason that (1) exposure may exist to several chemicals particularly in laboratories, (2) the quantitative data on exposure were not available and (3) some studies were negative, the evidence should be regarded as inadequate, at least in regard to exposure to solvents alone.
Case reports described serious malformations, more or less similar to the "fetal alcohol syndrome", particularly in women with excessive ("sniffing") exposure to solvents.
There was no evidence that specific organic solvents could be pinpointed as probable causal agents.

2.2.3 Birth weight/length and prematurity

Zielhuis et al (1984) already discussed two studies: Syrovadko et al (1977, USSR; see also 2.1 and 2.2.2) compared the body weight at birth of infants of 140 women exposed during pregnancy to toluene (25-140 mg/m^3) with that of infants of 201 non-exposed women. The average birth weight did not differ, although in the exposed group twice as many children were born with a birth weight of 2500-3000 grams ($p<0.02$). Postalache (1977, Poland, only available as summary, see also 2.1 and 2.2.2) reported a greater prevalence of prematurity in about 100 women exposed to acetate, butylacetate and toluene; most women also had non-specific symptoms of general toxicity. However, both reports lacked essential details; no conclusions can be drawn.

Nizyaeva (1982, USSR) observed in women exposed mainly to acetone (for intensity of exposure, see also 2.2.1) a decreased birth weight and length of the infants (in those exposed (E) $\leq$ 3000 g 39.4$\pm$4.3%; in the controls (C) 15.5$\pm$2.6%; ($p<0.001$); length for boys in E 51.7$\pm$0.3 cm, in C 52.4$\pm$0.3 cm; ($p<0.05$) and for girls 50.7$\pm$0.5 cm and 54.5$\pm$0.2 cm respectively; ($p<0.001$)).

However, insufficient details are presented to assess the validity of this study.

Axelsson et al (1984, Sweden, see also 2.1 and 2.2.1 and 2.2.2) studied the pregnancy outcome in female workers of a university laboratory. The average birth weight for pregnancies of women exposed to solvents during the second and third trimester 3456±522 g was according to the questionnaire; for unexposed pregnancies 3467±544 g. According to the Medical Birth Register birth weights were 3473±509 g and 3509±559 g respectively. The birth weight was not correlated with exposure to solvents and to work in laboratories, but for cigarette consumption (p±0.0005), gestational duration (p±0.0001), parity (p±0.0003) and sex of infant (p±0.0001) significant relations were established. No quantitative data on exposure to solvents were available.

Ericson et al (1984, Sweden, see also 2.2.2) studied the birth weight of the offspring of women working in laboratories during pregnancy. Comparing the deliveries of laboratory workers (1161 infants) with all deliveries (98354) recorded in the Medical Birth Register 1976 did not reveal any effect of exposure to solvents on birth weight and premature delivery.

Olsen and Rachootin (1983, Denmark) studied the birth weight and length of all 2620 healthy children delivered in Funen county in 1978-1979; for 2259 parent couples the sociodemographic, occupational background and reproductive history were obtained through a self-administered postal questionnaire. In four occupational groups with probable exposure to solvents (degreasers; exposure to lacquers, paint, glue; exposure to other organic solvents; exposure to cutting and lubrication oils) no effect on birth weight and length was observed.

Clarke and Mason (1985, UK, see for details 2.2.2) studied in female manual leather workers also the occurrence of immaturity; 5 cases (OR's=1.0-1.3); exposure probably took place to ethylacetate.

Discussion and conclusions

The seven available studies on birth weight/length and prematurity in relation with maternal occupational exposure to solvents do not provide any consistent evidence of an increased risk. It should be considered that the birth weight as reported by the mothers may differ from the weight registered in hospital records.

Axelsson and Rylander (1984, Sweden) compared questionnaire data and hospital records in their study of 782 female laboratory workers. In 28% the birth weight differed: the questionnaire data yielded 8% with a birth weight $\leq$ 50 g lower and 4.2% with >50g higher than recorded in the hospital register. Therefore, minor effects of exposure may become obscured. The overall causal evidence is inadequate.

2.2.4 Stillbirth and perinatal mortality

Syrovadko and Malysheva (1977, USSR; available as summary, see also 2.2.2) reported an increased perinatal mortality in deliveries of women exposed to vinyflex, chlorobenzene and tricresol. Mukhametova and Vozovaja (1972, USSR; quoted by Barlow and Sullivan, 1982; for details see also 2.1 and 2.2.1) examined 510 pregnant women: 250 gluers exposed to petroleum and chlorinated hydrocarbons and 260 controls. Incorrect implantation and detachment of the placenta was reported in respectively 8.8 and 4.2%; fetal asphyxia in 8.6 and 2.6%; perinatal mortality in 6.3 and 1.8%. Both studies present insufficient details to permit a valid conclusion.

Axelsson et al (1984, Sweden, see also 2.2.1 and 2.2.2) who studied the pregnancy outcome in university laboratory staff, also examined perinatal mortality. No increased risk was observed; no quantitative data on perinatal mortality were presented.

Ericson et al (1984, Sweden, see for exposure to solvents 2.2.2 and 2.2.3) compared 1161 deliveries of female laboratory (microbiological, research,

hospital and industrial) workers with all deliveries (n=98354) from the Medical Birth Register 1976. The results were as follows:

	lab. workers		all deliveries		
	%	n	%	n	
stillborn	0.95	11	0.56	548	
live born, death within 7 days	0.60	7	0.49	474	p<0.01
total perinatal deaths	1.55	18	1.04	1027	

The increase of the perinatal death rate was distributed between multiple and single births in such a way that in none of the two groups, considered alone significant differences were observed. Among 11 twin pairs three had a perinatally dead twin; moreover, another three twins died shortly after the 7th day; two of a triplet died perinatally. The perinatal death rate among singletons was 1,1 %; in all deliveries 0.95 %. Exposure to other chemicals and in some women also to microbiological agents also took place.

Clarke and Mason (1985, US; see also 2.2.2), who studied reproduction hazards in female manual leather workers with exposure to glues and ethylacetate observed a significantly increased Odd's Ratio of 2.6 (95 % CI 1.2-5.7; 17 cases) for macerated stillbirths.

Discussion and conclusions

Four studies present some evidence of an increased risk of stillbirth and/or perinatal mortality, however not confirmed by the fifth study. For the USSR-study detailed data on methods and designs were not available; the large scale Swedish study covered a multitude of exposures (Inter alia virus); the British study did not present data on the intensity of exposure. The overall evidence is considered as of 'low level' quality.

2.3 Risk of exposure of females with regard to the offspring (through lactation)

Syrovadko and Malysheva (1977, USSR, only summary available, see also 2.1.1 and 2.2.2 and 2.2.4) reported decreased appetite and even refusal of breast milk by infants of mothers exposed to chlorobenzene and tricresol, maybe due to a poor taste of the milk.

Bagnell and Ellenberger (1977, Canada) described a six week old suckling infant with obstructive jaundice; the breast milk contained 10 mg tetrachloroethene/l and 3 mg/l, 2 h respectively 24 h after the mother lunched with her husband in a dry cleaning shop. The levels appeared to be excessively high; no information was given on the concentration in inhaled air. It has not been established whether the icterus was due to the inhalation of tetrachloroethene.

Discussion and conclusions

Organic solvents are lipophilic. Consequently solvents are excreted in the (fat of) breast milk; the metabolites usually are excreted via the urine. Moreover, the study by Pellizari et al (1982) demonstrated the possibility for a wide range of solvents to be excreted in breast milk, even due to exposure at home or in the ambient environment, i.e. at much lower levels than in the occupational setting. No reliable data exist on potential health risks for the suckling infant. Follow-up studies of infants are needed.

2.4 Risk of exposure of males with respect to reproductive organs, endocrine system and fertility

2.4.1 Effects on sexual potency

Takeuchi et al (1972, Japan) reported a case of a worker exposed to organic solvents (mainly toluene, sometimes > 1000 ppm) in the paint industry. There were non-specific symptoms of drowsiness, slight fever, loss of weight, cramp in the lower extremities and impotence. Clinical examination revealed hypofunction of the hypothalamo-hypophysio-adrenal system, one-sided paraesthesia, abnormal EEG and some ortho-statism. The authors considered the

impotence to be the consequence of either the general malaise or of a specific effect on the nervous system. Saihin et al (1978, US) reported a case of a worker with symptoms and signs of impotence, gynaecomastia, neuropathy, scleroderma, malabsorbtion and Raynaud's phenomenon after longterm exposure to trichlorethene at work. The authors considered also other possibly causal factors; the role of trichloroethene was not conclusively established. Both case reports suggested a role of an altered hormone balance.

2.4.2 Effects on spermatogenesis and fertility

Suzuki et al (1983, Japan) presented a case history aspermia caused by thinner abuse. A 28 year old male died suddenly. He had been addicted to daily sniffing lacquer thinner since 10 years; there was no history of large consumption of alcohol.
The liver showed moderate fatty degeneration. The testis showed signs of atrophy: thickened tubular basement membranes lined with degenerative spermatogonia and Sertoli cells, faulty or suppressed spermatogenesis in the seminiferous tubules, which became smaller and further apart. A fatal concentration (43 mg/l) of toluene in blood was found; no alcohol was present. An observed liver disease may have played a causal role in the pathogenesis of testicular atrophy. It should be kept in mind that the daily exposure for 10 years very much exceeded the dose expected in exposure around the MAC-conditions.

Cook et al (1982, USA) carried out a cross-sectional study of white male, ethylene glycol monomethylether (EGME) process employees; potential exposure also existed to ethyl glycol ethylester (EGEE), polyols, polyoxypropyleneglycols, brake fluids, butylene glycol, polyglycols and organic amines. Since 1976 exposure (personal sampling) to EGME was 0.2 ppm, twa-8 h in the production area; rubber gloves were recommended. In 1980 exposure in the packaging and distribution building was 5.4 to 8.5 ppm, twa-8 h (Dutch MAC 5 ppm). The intensity of exposure was semi-quantitatively classified as "lower" (indirect and infrequent) and "higher" (packaging and laboratory). In the control departments (same plant, without exposure to EGME) exposure was possible to a variety of chemicals (inter alia phenol, ethylene glycol propylene ethers, ethylene oxide). Production of 1-2-dibrome-3-chloropopane (DBCP) had ceased in 1975. The total-scale study did not

eludicate any gross abnormalities or clinically meaningful differences between exposed and controls.

Rachootin and Olsen (1983, Denmark) studied the risk of infertility and delayed conception associated with exposure to solvents at work in 495 case couples examined or treated for a problem of infertility at Odense University Hospital in 1977-1980 and in fertile 2969 control couples with a healthy child born at the same hospital 1977-1979. Data on exposure and personal characteristics were obtained by means of a self-administered mailed questionnaire (response 87 %). The Odd's Ratio (OR) for men with sperm abnormalities or idiopathic infertility were for those potentially exposed to solvents as follows:

exposure	sperm abnormalities		idiopathic male infertility	
	OR	CI	OR	CI
degreasers	1.1	0.8-1.6	0.8	0.4-1.3
lacquer, paint, glue	1.2	0.9-1.7	1.1	0.7-1.8
other organic solvents	1.1	0.8-1.7	0.8	0.4-1.5
dry cleaning chemicals	1.0	0.5-2.0	0.2	0.0-1.4

Neither a relationship between the percentage of abnormal sperm counts of idiopatic infertility nor between delayed conception and exposure to solvents at work was observed. When the occupational titles were taken as indicator of potential exposure an indication of an increased percentage of abnormal sperm was found in the group of dry cleaners (tetrachloroethene?). However, not in man who held this job in the year prior to hospital admission, but only in those workers who had the longest occupational history in this very job; this may suggest an effect of the duration of exposure.

Savitz et al (1984, USA) carried out a survey of reproductive hazards among blue collar oil, chemical and atomic workers (OCAW), exposed to halogenated hydrocarbons (HC). They examined employees of 7 plants engaged in the

manufacturing and/or use of halogenated HC's and as controls those of 11 plants which produced vegetable oil and related products. The response rate was low: 41 % and 29 % respectively. This resulted in 1280 completed questionnaires. In the plants exposure was possible to ethylene dichloride, methylchloride, tetrachloroethene and to vinylchloride, chlordane and epichlorohydrin. OCAW representatives rated the divisions as L(ow) or H(igh) exposure. The duration of employment differed between exposed and non-exposed workers: respectively 56 % (L), 41 % (H) and 28 % of non-exposed workers were employed for at least 10 years. The relative fertility rate (per 100 respondents) was: L-RR=18.2; H-RR=1.72 for prehire (X^2 trend 2.80, p=0.047) and 0.96 and 1.64 for post-hire (X^2 trend 3.33; p=0.034) respectively. The authors considered these trends as not-significant because of absence of an exposure-response relationship and the poor response.

Rosenberg et al (1985, USA) studied the sperm as an indicator of reproductive risk among petroleum refinery workers. The plant refined motor fuels, lubricants and specialty products such as asphalt. Workers of the waste water treatment plant (operatives since 1976), which purifies water contaminated mainly by organic compounds, were considered exposed (n=42) if they had been working at least 6 months before the study (overall participation 68 %). Unexposed workers (n=74) were selected from other refinery workers (n=100) and administrative personnel (n=100, overall participation 44 %). Sperm was sampled after at least two days abstinence. Potential confounders were other occupational exposure, use of prescribed drugs, abnormal medical history, smoking, addiction to marijuana, consumption of alcohol, age and days of sexual abstinence. Even although the sperm count and morphology were considered sensitive indicators of the spermatogenic function no difference was observed between exposed and controls. The power was sufficient to have a 80 % chance to detect a 7.3 % increase of abnormally shaped sperm, and a decrease of 39 % of the sperm concentration. No data were presented on actual exposure to organic solvents, whereas exposure to insufficiently specified other agents also occurred.

Tuohimaa and Wickmann (1985, Finland) studied the sperm production of 11 men (age 23-46 yrs) of a printing factory where multiple solvents exposure occurred to ethanol 1000 ppm (Dutch MAC 1000), ethylacetate 150 ppm (400),

oxytol 10 ppm (no Dutch MAC; Finnish MAC 100), white spirit 50 ppm (100) and isopropanol 150 ppm (400). No effect on sperm-count and -motility was observed.

Discussion and conclusions

The few studies available do neither suggest an adverse effect on the reproductive organs (spermatogenesis) nor on fertility in male workers exposed to solvents at work. Excessive exposure (addiction) may probably lead to testis atrophy and aspermia, at least in exposure to toluene and maybe to hepatotoxic solvents (e.g. carbon tetrachloride, chloroform) when overexposure leads to moderate liver disease. Moreover, libido and sexual potency may be adversely affected at exposure above the MAC as a non-specific aspect of general narcotic effects of solvents or of a specific effect on the nervous system such as the hypothalamo-hypophysio-adrenal axis (Gennart and Lauwerys, 1985).

The overall evidence for absence of effects on reproductive organs, endocrine system in male workers exposed to solvents below or around the MAC-levels has to be considered as inadequate; that for the absence of effects on fertility is limited.

2.5 Risk of exposure of males with respect to pregnancy and offspring of the partner

2.5.1 Spontaneous abortion

Savitz et al (1984, USA, see 2.4) did not observe any evidence of increased fetal loss (low response).

Morgan et al (1984, USA) studied fetal loss in 101 spouses of workers employed in a waste-water treatment plant (WWTP) of a mayor oil company. The spouses were personally interviewed through a fairly rigid standardized questionnaire. The WWTP-employment histories of the male workers were collected from company records. The workers were exposed to many chemicals including solvents, albeit most at low concentrations. The total number of pregnancies to which a WWTP-exposure category (E:1 any time before conception, E2: within 4 months prior to conception, E3: $\leq$3 months after conception) could be assigned, was 220. The relative risks (RR) and 95 % confidence intervals (CI) for miscarriage and/or

stillbirth were calculated by comparison with the pregnancy outcome of the partners of non-exposed workers:

exposure category	RR	95 % CI	P
E1	2.05	0.93-4.52	0.07
E2	2.86	1.30-6.29	0.008
E3	2.94	1.35-6.40	0.006

This study did not reveal a decreased fertility, but it suggested an increased fetal loss rate, although not different between workers exposed before (E1, E2) or after (E3) conception. Therefore, no exposure-response relation is observed. It is surprising that the RR after conception (E3) is even the highest. There was exposure to many other chemicals. On the other hand an RR of 5 for spontaneous abortion was observed among a subgroup of WWTP workers (mechanical instrument workers and electricians), although the small sample limited the conclusions. Moreover, even if there had been an effect on the male gametes, this need not to be due to exposure to solvents. Wong et al (1985, USA) recalculated the data over 1976-1981 (n=55 workers, total person-years 145); the Standard Birth Rate (SBR) appeared even to be significantly increased when the expected rate was based on US national fertility rates ($p<0.01$); however, comparison of a small group with the national average may easily lead to erroneous conclusions.

Lindbohm et al (1984, Finland, for details see 2.2.1) analysed the rate of abortion among the wives of husbands according to male occupational exposure to solvents and other chemicals. Analysis of the age-standardized rates revealed four occupations (metal-plate and constructional steel workers; crushers, grinders, calandar operators; sewers, leather garments, glove production; workers taking care of fur-bearing animals) with a significantly increased risk ($p<0.01-<0.05$). However, the group with a non-significantly increased risk (OR=1.64; 95 % CI 0.95-1.64) was that of service station attendants, which at face value might have had most exposure to solvents (petrol).

The overall evidence of absence of risks of spontaneous abortion by paternal exposure to solvents at work, should be regarded as inadequate.

2.5.2 Congenital malformations

Olsen (1983, Denmark, see 2.2) examined the risk of exposure to teratogens amongst laboratory staff and painters. The relative prevalence rate (RR) for congenital malformations in stomach/intestinal canal, extremities and lip/palatal cleft could not be defined for fathers' occupation (mothers' occupation RR=1.3). The RR for defects of the central nervous system was 2.8 (95 % CI=0.8-9.4) in the offspring of fathers working in the printing industry, as a painter or as a flooring operator or a linoleum layer (exposure to solvents for mothers not defined); for fathers as painter the RR was 4.9 (95 % CI=1.4-17.1) (for mothers not defined). Unskilled or semi-skilled male workers exposed to solvents had a significantly higher risk (RR=1.9) (95 % CI=1.2-3.2) of fathering a child with CNS-defects than skilled workers, although for all workers the RR=2.8 was not significant. The fact that a significantly higher risk of central nervous system malformations was observed if the father was a painter was (according to the author) indirectly supported by the association observed between painting and solvent exposure and brain tumors in children. No quantitative data on exposure were available.

In the study by Savitz et al (1984, USA, see also 2.4.2, low response) of workers exposed to halogenated HC's no increased risk of congenital defects were observed.

The evidence of an increased risk of congenital abnormalities by male exposure should be regarded as inadequate, because of the few studies available on the conflicting results.

2.5.3 Birth weight and length

Olsen and Rachootin (1983, Denmark, see also 2.2.3) studied the effect on birth weight and -length of the children of exposed women and/or their spouse to solvents in using degreasers, lacquers/paints/glue, cutting and lubricating oils and other organic solvents. No effect of either maternal and/or paternal exposures was observed. The evidence for an effect on birth weight and length should be regarded as inadequate.

3. DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS HUMAN DATA

This review of literature did not assess the human data for each solvent separately, since it was expected that such an approach would not yield any substantial results. This was confirmed by this study.
The overall causal evidence reviewed has been summarized in Table 3. In addition solvents are excreted in breast milk, when exposed during lactation, also when exposed far below the MAC's. This constitutes at least a potential health risk for the infants when drinking breast milk contaminated with solvents have been found in literature.

Exposure data

- Most data refer to combined exposure; tetrachloroethene may be regarded as a solvent which at least in chemical cleaning shops is applied as the major chemical compound, although some other chemicals may also be present in workroom air.
- In several studies also exposure to other chemicals, not to be regarded as solvents, were present; often these chemicals were even not specified.
- The assessment of intensity and duration of exposure to solvents was often deficient, although recent studies sometimes contained (semi)quantitative data, which permitted an estimation exposure exceeded the present TLV/MAC's.
- In hardly any study biological monitoring was applied for the assessment of internal exposure. Because of the comparatively short half life of most solvents, biological monitoring data should be based on repeated measurements.

Study design

- The large majority of studies was retrospective; this particularly is a drawback in studies on solvents, because of the usually rather short biological half lifes. The rather long half life of tetrachloroethene is of advantage in studies in chemical cleaning shops.
- Various studies were on large scale (nation-wide, regional, branch of industry), others where on small scale. This leads to a paradox: large scale studies may be statistically more sensitive, but the quality of exposure data generally is poor and therefore is less specific, whereas small scale studies are less sensitive, but may be more specific, because of the better

quality of the exposure data and because more attention can be paid to confounding factors.

- The specificity of self reported data on epidemiologic endpoints appears to be less than when the data are obtained from e.g. Hospital Registers. In the self reporting memory bias may play an unknown role; induced abortion may not be reported wilfully. In several studies no data on induced abortions were available at all. In some studies only clearly definable malformations were taken into account; this increases the specificity, but decreases the sensitivity of the study.
- Many studies paid too little attention to confounding factors, which are related both to exposure to the potential causal factor and to the reproductive endpoint studied or to contributing factors which increase the prevalence of reproductive risks. A few examples may illustrate this. There exists a negative relation between the socio-economic status (SES) of female workers and the quality of the working environment (more unfavourable working conditions, including exposure levels) and the increased prevalence of unfavourable endpoints on reproduction (Mammelle et al, 1984; Slob, 1986). Also associated with the SES are unfavourable life style factors as e.g. nutritional habits, consumption of tobacco and alcoholic drinks. Little (1986) observed increased prematurity and a lower birth weight of the newborns of mothers who consumed alcohol before or during pregnancy. Sufficient evidence exists on the negative effects of smoking on reproduction. Life style factors may differ between exposed and reference groups. Only relatively few of the reviewed studies provide data on life style factors and overall working conditions.
- Particularly large scale studies, relying on e.g. occupational titles or union memberships usually assume that all workers defined as exposed are exposed to solvents to a similar degree although an unknown percentage may not or to a much smaller degree be exposed. This leads to a dilution of the exposed group and consequently to an underestimation of the relative risks.
- The most informative studies have been carried out in highly developed countries with probably more favourable exposure levels than in may less developed countries. This does not exclude the possibility that at high exposure levels increased reproductive risks may occur.
- Some studies are of a relatively poor design. When several studies show consistent trends, e.g. in the case of menstrual disorders, then one cannot

reject such evidence. One should consider this trend as at least of low level evidence.
- There is an urgent need to carry out prospective studies in which external and internal exposure should periodically be assessed quantitatively and in which the endpoint can be verified. The statistical power of the study should be established.

epidemiologic endpoints

- A large number of epidemiologic endpoints have been studied. However, most studies paid attention only to one or a few endpoints. No studies examined the full range, e.g. in females: menstrual disturbances, infertility, abortion, toxaemia, malformation, praematurity, birth weight/length, perinatal mortality/-morbidity, development of infant cancer of reproductive organs.
- Only very few studies are available on reproductive effects through exposure of male workers.
- It was never possible to exclude effects.
- There is an urgent need to study a large range of reproductive endpoints in future studies; this will increase the sensitivity of the study and may increase the knowledge of working mechanisms.

Causal evidence

The degree of causal evidence was distinguished into four groups, according to Hemminki et al (1985) (Table 3).

The causal evidence of a relation with exposure to solvents is considered to be low level or inadequate for the large majority of endpoints on reproduction effects; some studies did not reveal any effect at all. Nevertheless, a causal role cannot be excluded. Some studies showed some evidence of a positive exposure-response relationship; this e.g. applies to exposure to female workers with spontaneous abortion.

There exists limited causal evidence that in exposure of female workers there may be adverse effects on menstruation, malformation (particularly orofacial cleft). The endpoints for which there exists limited or low level evidence of an increased risk deserve priority in future research.

The potential risk to infants who receive contaminated breast milk certainly deserves further study both in regard to the acceptance of breast milk by the infant and to potential effects on growth and development.
A few studies indicate an increased relative risk in exposure to a few specified solvents, e.g. tetrachloroethene, petroleumether, methylene chloride. However, it cannot be established whether this is a question of chance, of relatively high exposure mainly to the specified solvent or of a specific effect of these solvents.

The working mechanism

The general working mechanism of solvents is not known; it may be a direct effect of the solvent or its metabolite on the gametes, on the reproductive organs, on the fetal/uterus system during pregnancy or on the developing infant. There also may exist an indirect effect on the endocrine system, the normal function of which is essential for the fertility and undisturbed pregnancy. Moreover, it is also possible that genotoxic and/or somatotoxic effects may be induced in the fetal stage.
One usually classifies health effects of solvents as follows:

- non-specific effects particularly on the nervous system and the skin, which are common to all solvents, albeit different in intensity, and
- specific effects on specific organ systems, e.g. liver and hematopoetic system.

It can be postulated that the non-specific effect on the central nervous system may affect the endocrine balance through the hypothalamo-hypophysioadrenal axis. Only a few studies, discussed in this review, pointed to a disturbed endocrine balance. This aspect certainly deserves more attention in future research.

4. REVIEW OF ANIMAL DATA

4.1 ACETON

4.1.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility and offspring

No data available.

4.1.2 Risks of exposure of female animals with respect to gestation and prenatal development

Nizyaeva (1982) exposed pregnant female animals to acetone by inhalation. Unfortunately, the species was not mentioned. The female animals were exposed in a first experiment to 0 mg/m3 (N=24), 30 mg/m3 (N=25) and 300 mg/m3 (N=20) on days 1-13 of gestation. In a second experiment animals were exposed to 0 mg/m3 (N=26), 30mg/m3 (N=21) and 300 mg/m3 (N=23) on days 1-20 of gestation. The results are summarized as follows:

	Number of implantations	postimplantation loss	number of live foetuses
Days 1-13 of gestation			
30 mg/m3		inc* (P<0.01)	
300 mg/m3			
Days 1-20 of gestation			
30 mg/m3		inc (P=0.01)	red (P<0.001)
300 mg/m3	red** (P<0.05)	inc (P=0.002)	red (P=0.002)

inc*: increased; red**: reduced.

4.1.3 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the partner and offspri-

No data available.

4.1.4 Risks of exposure of both male and female animals (mating partners) with respect to gestation and offspring

No data available.

4.1.5 Conclusion animal data

With respect to gestation and prenatal development (4.1.2) the only paper available suggest that acetone is embryotoxic. However, the available data are insufficient to draw any conclusion. Risks of exposure to female and or male animals with respect to gonads, endocrine system, fertility, gestation of the partner and the offspring can not be evaluated since data are lacking.

4.2 Tertiary Butanol ISN 20656

4.2.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility, gestation and prenatal development

No data available.

4.2.2 Risks of exposure of female animals with respect to the offspring

Daniel et al. (1982) fed liquid diets containing tertiary butanol to groups of 15 mice in concentrations of 0, 0.50, 0.75 or 1.00 % from day 6 to day 20 of gestation. Within 24 hr after parturition the litter data such as number of litters, litter size, average weights, and the number of deaths were recorded.

At doses of 0.75 and 1.00 % t-butanol, litter data were affected as was observed by a decreased umber of litters, decreasing litter size, decreased postnatal weight gain, and an increased number of stillborn. Eye opening was delayed in the 1.00 % t-butanol group and occurred around day 16, instead of day 12 to 14 as was observed in the other groups. During postnatal development, righting reflex, and open field activity were affected in the 0.75 % and 1.00 % groups. The NAEL was 0.50 %.

4.2.3 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the partner and the offspring

No data available.

4.2.4 Risks of exposure of both male and female animals (mating partners) with respect to gestation and to the offspring

No data available.

4.2.5 Conclusion animal data

Sufficient data are lacking to draw a well documented conclusion as to the effects of t-butanol on fertility and reproduction in laboratory animals. A NAEL could not be assessed.

4.3 2-BUTANONE (METHYLETHYLKETONE) ISN 20657

4.3.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

No data available.

4.3.2 Risks of exposure of female animals with respect to gestation and prenatal development

Schwetz et al. (1974) exposed rats to 0, or 2980 mg/m3 (N=23) and 0, or 8940 mg/m3 (N=21) methylethylketone for 7 h/day on days 6-15 of pregnancy. The data from the 2 control groups (N=43) were combined for statistical comparison with the exposed animals for all parameters except for the incidence of delayed ossification of sternebrae. Exposure of rats to either of the dose levels of methylethylketone had no effect on maternal weight gain during gestation. There was no effect on the conception rate, number of implantations, litter size, serum glutamic pyruvic transaminase activity (parameter of maternal hepatotoxicity), and absolute or relative maternal liver weights. Methylethylketone had no effect on the incidence of fetal resorptions. At 2980 mg/m3, fetal body weight, being 5.34 g, and crown-rump length, being 42.3 mm, were significantly decreased when compared with the controls (5.64 g and 43.7 mm). However, these changes were not observed in rats exposed to 8940 mg/m3 methylethylketone. Therefore, these changes are not considered to be treatment related. A significantly increased incidence of litters containing fetuses with skeletal anomalies (of any kind) was observed at 2980 mg/m3, but the increase was not significant at 8940 mg/m3, 95 % and 81 % of the litters of the low and high dose group respectively were affected against 58 % in the control. According to the authors the incidence of sternebral anomalies (bipartite; delayed ossification) was significantly increased in the fetuses exposed to 8940 mg/m3 methylethylketone. However, the incidence of sternebral anomalies varied considerably in both control groups, being relatively low (11 % of litters affected) in the control group paired with the 8940 mg/m3 group (43 % of the litters affected), but in the control group paired with the 2980 mg/m3 group the incidence was higher than in the group exposed to 8940 mg/m3 (43 % of the litters affected in 8940 mg/m3 group versus 61 % of the litters affected in the controls). Therefore, this finding may be of questionable biological significance. There were four litters containing fetuses with gross anomalies (2 acaudate fetuses with an imperforate anus and 2 brachygnathous fetuses), against 0 in controls, which was statistically significant ($P<0.05$). The overall incidence of soft tissue anomalies was significantly higher at 8940 mg/m3 with 76 % of litters affected compared with 51 % of litters in controls.

John et al. (1980)-abstract- exposed rats (N=?) by inhalation to 0, 1192, 2980 or 8940 mg/m3 methylethylketone for 7 hr/day on days 6 through 15 of gestation. Minor fetotoxicity was observed in litters of rats exposed to 8940 mg/m3 as evidenced by an increased incidence of two minor skeletal variants. Deacon et al. (1981) exposed rats to 0 (N=35), 1192 mg/m3 (N=25), 2980 mg/m3 (N=25) or 8940 mg/m3 (N=25) methylethylketone for 7 hr/day on days 6 through 15 of gestation. Maternal toxicity was observed among rats exposed to 8940 mg/m3 by decreased weight gain and increased water consumption. No changes were observed in maternal liver weight, or in food consumption of pregnant rats (no data are given in the paper). No effects were observed with regard to embryotoxicity, such as an increased incidence of resorptions or pre-implantation loss. A significant ($P<0.05$) decrease in the incidence of delayed ossification of interparietal bones of the skull was noted among litters of rats exposed to 8940 mg/m3. A significant increase ($P<0.05$) in the incidence of extra lumbar ribs and the occurrence of delayed ossification of skull and cervical centra was also noted at this exposure level.
Since the applied dose levels, the observed effects and even some authors are identical to the study reported by John et al. (1980), the two papers might describe the same study.

4.3.3 Risks of exposure of female animals with respect to the offspring

No data available.

4.3.4 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the parter and offspring

4.3.5 Risks of exposure of both male and female animals (mating partners) with respect to gestation and the offspring

No data available.

4.3.6 Conclusion animal data

With respect to risks of exposure of female animals with respect to the gestation and prenatal development (4.3.2) there may be a small increase in major malformations and a delay in the ossification of fetal bones, among litters of rats exposed to 8940 mg/m3 of methyl ethyl ketone. Other findings on embryotoxicity and teratogenicity at 2980 mg/m3 and 8940 mg/m3 are difficult to evaluate since, on the basis of the two available studies the data are conflicting and not dose-related. From the very scarse data on methyl ethyl ketone, it appears that in rats the NAEL is at least 1192 mg/m3, which is well above the current MAC (590 mg/m3).
With respect to effects on reproductive organs, endocrine system, fertility, and on the offspring after exposure of females and/or males, there were no data available.

4.4 CARBON TETRACHLORIDE ISN 20658

4.4.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

Levin et al. (1970) studied the effect of carbon tetrachloride on the metabolism and activity of estradiol-17B and estrone in the rat. Female rats (N=?), 19 to 20 days old, were pretreated orally with carbon tetrachloride (0.17-1.7 ml/kg) in 0.1 ml corn oil, or with the vehicle only. Twenty-four hours later tritium labeled estradiol-17B or estrone was administered i.p. in 0.20 ml of a solution containing 10 % ethanol in saline. The rats were killed by decapitation at various times after the injection. The inhibiting effect of carbon tetrachloride on drug-metabolizing enzymes was reflected by a potentiation of the uterotropic action of the oestrogens as measured by a significant increase of the uterine wet weight ($P<0.05$) and by an increased amount of tritiated estrogen in the uterus. The authors suggest, that estradiol-17B is metabolized extensively to estrone and that carbon tetrachloride may inhibit the further metabolism of estrone to polar metabolites. Hepatic damage was determined by measuring Glutamic Pyruvic Transaminase Activity (SGPT) 24 hours after a single dose of various amounts

(0, 0.03, 0.17-1.7 ml/kg) of carbon tetrachloride. The 7- to 24-fold increased SGPT activity illustrate the extreme potency of carbon tetrachloride as a hepatotoxic agent.

Khominska (1974)-see Barlow et al. 1982-injected female rats s.c. with 3 ml/kg of carbon tetrachloride, 4 times on one day. Nature and duration of the oestrus cycle was examined during one month after the treatment. There was a significant (P=?) increase in the mean duration of the cycle from 4.56 to 5.21 days and the oestrus phase was prolonged with more than one day.

Feuer et al. (1979) studied the effect of carbon tetrachloride on the hepatic and serum levels and metabolism of progesterone. Carbon tetrachloride was injected as a single dose or as 4 daily i.p. doses of 5.2 mmol/kg (0.5ml/kg), dissolved in arachis oil. The last injections were given 18 h before sacrifice. Ten minutes before the animals were sacrificed [4-14C] progesterone diluted in physiological saline was injected i.v.. Animals in anestrus phase were not included in this study. There were 4 animals in each group.

Treatment of rats with carbon tetrachloride resulted in a significant ($P<0.05$) reduction of serum progesterone levels (in the estrus cycle phase, but not in the diestrus cycle phase) and a reduction of hepatic progesterone levels. There was a significant reduction in the incorporation of [4-14C] progesterone in the liver (73.4 nCi/g tissue against the control value of 289.7 nCi/g tissue). There was also a significant ($P<0.05$) reduction in the total amount of progesterone present in the liver and serum of carbon tetrachloride-treated rats. Carbon tetrachloride shifted progesterone metabolism to the reductive pathway as it caused a significant ($P<0.05$) decrease of hydroxylation and an increase of hydrogenation.

Summary of the risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility.

Species	exposure	dose	effects	Ref.
rat	single	0.17-1.7ml/kg oral	increased uterus weight, inhibition of estrogen metabolism, hepatoxicity	Levin et al. (1970)
rat	24 hours	3 ml/kg, s.c 4 times	increase in the duration of the oestrous cycle	Khominska (1974) (a).
rat	not clear	5.2 mmol (0.5 ml/kg),i.p.	decreased progesteron level, altered progesteron metabolism	Feuer et al. (1979).

(a) see: Barlow et al. 1982

4.4.2 Risks of exposure of female animals with respect to gestation and prenatal development

Administration by inhalation

Gilman (1971) (abstract) exposed rats (N=?) by inhalation to 1575 mg/m3 carbon tetrachloride vapour, 8 hr/day from day 10-15 of pregnancy. Carbon tetrachloride did not reveal significant effects on weight changes, live vs still births, litter size, resorptions, viability index, lactation indices and skeletal abnormalities.

Schwetz et al. (1974) exposed rats to 0 (2 times), or 1890 mg/m3 (N=22) and 0, or 6300 mg/m3 (N=23) carbon tetrachloride for 7 h/day on days 6-15 of pregnancy. The data for the 2 control groups (N=43) were combined for statistical comparison with the exposed animals for all parameters except the incidence of delayed ossification of sternebrae. At 1890 and 6300 mg/m3 food consumption was significantly ($P<0.05$) reduced throughout the 10-day exposure

period and maternal body weight was significantly ($P<0.05$) lower by day 21 when compared with the controls. There was no effect on the conception rate, the number of implantations or litter size. Evidence of maternal hepatotoxicity was seen in both groups; serum glutamic pyruvic transaminase (SGPT) was significantly ($P<0.05$) elevated during exposure, but had returned to normal by day 21 when relative liver weights were significantly ($P<0.05$) increased but absolute weights were unchanged. Carbon tetrachloride had no effect on the incidence of fetal resorptions. At both dose levels fetal body weight, being 5.29 and 4.96 g in the low- and high dose group respectively, and crown-rump length, being 42.2 and 42.8 mm respectively, were significantly decreased when compared with the controls (5.64 g and 43.7 mm). According to Barlow et al. (1982) this is not unexpected in view of the severe effect on food consumption in the dams. A significant increased incidence of subcutaneous edema was observed at 1890 mg/m3, but the increase was not significant at 6300 mg/m3, (59 % and 50 % of the litters of the low and high dose group respectively were affected against 33 % in the control). According to the authors the incidence of sternebral anomalies (bipartite; delayed ossification) was significantly increased in the fetuses of rats exposed to 6300 mg/m3 carbon tetrachloride. However, the incidence of sternebral anomalies varied considerably in both control groups, being relatively low (11 % of litters affected), in the control group paired with the 6300 mg/m3 group (59 % of the litters affected), but in the control group paired with the 1890 mg/m3 group the incidence was as high as in the group exposed to 6300 mg/m3. (59 % of the litters affected in 6300 mg/m3 group versus 61 % of the litters affected in the controls).

In view of the observed maternal toxicity already present at the lowest dose and the conflicting result with the incidence of sternebral anomalies it might be concluded that the dosages applied were too high.

Leong et al. (1974)-abstract paper- exposed rats (N=?) to 300 ppm (1890 mg/m3) and 1000 ppm (6300 mg/m3) for 7 h/day from days 6 through 15 of pregnancy. The compound caused minor retardation of fetal development as expressed by a delayed ossification of sternebrae.

Since both the applied dose levels, the observed effects and the names of the authors were identical to the study reported by Schwetz et al. (1974), this may be the same study.

Administration by injection

Tsirelnikow et al. (1973) studied the effect of carbon tetrachloride on the liver of offspring of treated rats (total number of used animals 34). The control group consisted of 30 animals. The rats received 3 ml/kg carbon tetrachloride (injection method not specified) on one of days 12-22 of pregnancy and were sacrificed 48 hours later. After administration on the 12th-15th day of pregnancy death of the fetuses occurred in most cases (no data). In the groups treated on one of days 16-22 fetal body weight was significantly lower than in controls. Treatment on the 16th day revealed relatively lower fetal liver weights (2.83 mg) in comparison with controls (6.6 mg, $P<0.001$). However higher fetal liver weights were observed in groups treated on day 18 (8.86 mg versus 8.19 mg in the controls, $P<0.05$), day 21 (9.37 mg versus 7.47 mg in the controls, $P<0.05$) and day 22 (7.37 mg versus 5.87 mg in the controls, $P<0.05$). There is no explanation from the authors about the phenomenum. In the fetal liver, morphological changes were not seen on the 15th-18th day, but from the 18th day of development an increased hematopoietic tissue activity as compared with control fetuses was observed. On the 16th day, in the liver of the embryos of the treated group, the content of acid and neutral lipids was raised, reaching a maximum towards the end of fetal development (no data). The appearance of glycogen was delayed by one day: on day 19 instead of day 18, and in most cases the glycogen content in the hepatocytes remained low at the end of foetal development (no data). The authors mentioned, that at the end of pregnancy, the severity of damage to the fetal liver was less than effects on the maternal liver.

Kyutukchiev et al. (1971)-see Barlow et al. 1982-also demonstrated relative protection of the fetal liver to the toxic effects of carbon tetrachloride. They injected rats (N=?) with 0.3 ml/kg i.p. on day 13 or 17 of pregnancy and killed the animals on day 16 or 20 respectively. Changes in liver enzyme levels (not indicated which enzymes measured, and no data) were more marked in the mother than the fetus.

Khominska (1974)-see Barlow et al. 1982-injected female rats (N=?) s.c. with 3 ml/kg of carbon tetrachloride, 4 times on one day. Next, the animals were mated not earlier than 7 days after the injections. Pre-implantation loss was increased from 5 % in controls to 21 % in treated dams, and post-implantation loss was increased from 7 % in controls to 18 % in treated rats. In the fetuses, corticosterone levels in the treated group were twice as high as control levels (no data presented), which was attributed to possible hepatic damage in the fetuses.

Summary of the risks of exposure of female animals with respect to gestation, and prenatal development.

Species	exposure	dose	effects	NAEL	Ref.
rat	day 10-15 of pregnancy	1575 mg/m3/ 8h/day inhalation	none	1575 mg/m3	Gilman (1971)
rat	day 6-15 of pregnancy	0, 1890, 6300 mg/m3/7h/day inhalation	decreased food consumption and body weight dams,increased liver weight dams, decreased fetal body weight and decreased crown-rump length	<1890mg/m3 7h/day	Schwetz et al. (1974)
rat	day 6-15 of pregnancy	0, 1890,6300 mg/m3/7h/day inhalation	retarded developm. fetus	<1890mg/m3 7h/day	Leong et al. (1974)
rat	day 15-22 of pregnancy	3 ml/kg single inject. s.c. or i.p.?	embryonal death, decreased weight fetus, increased and decreased liver weight fetus.	<3ml/kg	Tsirelnikov et al. (1973)
rat	day 13 or 17 of pregnancy	0.3 ml/kg i.p.	enzymatic changes in liver of dams and fetuses	<0.3ml/kg	Kyutuk-chiev et al. (1971) (a)
rat	on the 7th day prior to mating	3 ml/kg s.c.	pre-and post-implantation loss	<3 ml/kg	Khominska (1974) (a)

(a) see: Barlow et al., 1982

4.4.3 Risks of exposure of female animals with respect to the offspring

No data available.

4.4.4 Risks of exposure of male animals with respect to the reproductive organs, endocrine system and fertility

Kalla et al. (1975) injected male rats (N=?) i.p. with a mixture of carbon tetrachloride and coconut oil. The dose of carbon tetrachloride was 1.5 ml/kg body weight. The treatment was given for 10, 15 or 20 days (three groups of animals) and the animals were sacrificed 24 h after the treatment. A decrease in the weight of the animals, the weight of the testes and accessory sex organs (seminal vesicles, epididymis, prostate) was observed in all three groups. The weight of the adrenal was increased in the three groups. Histological examination of the testis did not reveal any significant damage in the 10 day-treatment group. However, there was a slight effect on the spermatogenesis (spermatogonic cells were reduced in number and seminiferous tubules were dilated) in the 15 day-treatment group. After 20 days of treatment severe damage of the spermatogenic cycle was observed, leading to exfoliation of the germinal epithelium, depletion of germ cells, and shrinkage of seminiferous tubules.

4.4.5 Risks of exposure of male animals with respect to gestation of the female, and to the offspring

No data available.

4.4.6 Risks of exposure of both male and female animals (mating partners) with respect to gestation and the offspring

Alumot et al. (1976) carried out a preliminary study in which groups of six weanling rats were fed diets containing 150, 275 or 520 ppm for 6 weeks (males) or 5 weeks (females) at the end of which the animals were killed. Carbon tetrachloride at 520 ppm induced depressed weight gain in the males

($P<0.05$). In the 275 ppm and 520 ppm groups there was a significant ($P<0.01$) increase of fat in the liver. The reproductive activity of male and female rats was not affected by carbon tetrachloride.
On the basis of this preliminary study Alumot et al. carried out a chronic study (2 years) with carbon tetrachloride at levels of 0, 80 and 200 ppm in the diet given to male and female rats. Each treatment group consisted of 18 females and 9 males. The administration started two weeks after weaning. After 6 weeks on the experimental diets, the (3-month-old) females were mated with untreated males to test their reproductive capacity.
Thereafter the females were mated, at about 2-monthly intervals, with treated males for 4 successive pregnancies. No adverse effects attributable to either treated males or treated females were seen in terms of pregnancy rate, delivery rate, live litter size, offspring weight or mortality. After 2 years the surviving animals were killed and biochemical tests did not reveal any effect either on liver function, as indicated by transaminases and cholesterol values, or on kidney function, as shown by the urea and uric acid levels. No fatty livers were detected in the treated animals.
It was calculated, that at the end of the chronic study the actual carbon tetrachloride intake in the 200 ppm concentration ranged from 10 to 18 mg carbon tetrachloride/kg body weight/day. At this level no (observable) liver damage or effects on body weight could be observed. On the basis of these data, the authors propose acceptable daily intakes of 10 mg/kg body weight for carbon tetrachloride.

4.4.7 Conclusion animal data

With respect to risks to the endocrine system (4.4.1) at exposure of female animals it can be concluded, that carbon tetrachloride affects the estrogen metabolism. Although there are hardly sufficient data to set a NAEL, the tendency is that in rats the NAEL is < 0.17 ml/kg and < 0.5 ml/kg after respectively oral and i.p. injection.
With respect to risks on fertility (4.4.1) no data were available.
With respect to risks on gestation and prenatal development (4.4.2) also only a few data are available. In the rat (the only species tested) carbon tetrachloride does not seem to be teratogenic but may be embryo- and fetotoxic

at doses that are also toxic to the dam. The mechanism of embryotoxicity may be induction of placental damage (Barlow et al. 1982).
With respect to risks on the offspring (4.4.3) after exposure of female animals no data were available.
With respect to risks on sexorgans, endocrine system and fertility (4.4.4) after exposure of males only one paper is available. After i.p. injection of 3 ml/kg with a treatment period of 10 days no significant damage to spermatogenic cycle was observed, but at intervals of 15 and 20 days severe damage of the spermatogenic cycle was present. At all intervals the weight of the testis and accesory sex organs was decreased.
With respect to risks on gestation of the female and progeny after exposure of males (4.4.5) no data were available.
With respect to risks on gestation, and progeny after exposure of both males and females (mating partners) (4.4.6) an acceptable daily intake may be 10 mg/kg body weight, which is equivalent to 100 ppm in the diet (Alumot et al., 1976). On the basis of a NAEL of 10 mg/kg body weight, the calculated intake is 8 mg/m3, which is close to the present MAC value of 12,6 mg/m3.

4.5 CYCLOHEXANOL ISN 20660

4.5.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility, gestation, prenatal development, and the offspring

No data available.

4.5.2 Risks of exposure of male animals with respect to the reproductive organs, endocrine system and fertility

Tyagi et al. (1979) tested cyclohexanol for its anti-spermatogenic activity in gerbils and rats.Twenty adult gerbils and twenty rats were injected (s.c.) with 15 mg/kg/day for a period of 21 and 37 days respectively. Equal numbers of controls received distilled water. The animals were killed twenty-four hours after the administration of the final dose. Cyclohexanol administration did not change body weight, thyroid weight and adrenal weight (the data were

not presented in the paper). In the gerbil a significant reduction was noticed in the weight of testes ($P<0.01$), epididymides ($P<0,001$) and ventral prostate ($P<0.01$). In the rat the weight of testes ($P<0.001$), epididymides ($P<0.001$), seminal vesicles ($P<0.01$) and ventral prostate ($P>0.01$) were reduced significantly. In the testes the seminiferous tubules presented marked degenerative changes. Shrinkage of the seminiferous tubules and Leydig cell nuclei were noticed in both animal species. The observed degenerative changes were loss of type A spermatogonia, spermatocytes, spermatids and spermatozoa. In both treated animal species total protein, RNA and sialic acid contents of the testes, epididymides and seminal vesicles were lower ($P<0.01$). The cholesterol contents and the phosphatase activity of the testes were higher than in controls ($P<0.01$), whereas glycogen contents were reduced ($P<0.01$) after cyclohexanol treatment. Haematological parameters in gerbils and rats treated with cyclohexanol were not affected.

Dixit et al. (1980) tested cyclohexanol for its anti-spermatogenic activity in the rabbit. Group 1 ($N=5$) served as control, whereas group 2 ($N=5$) and group 3 ($N=5$) received cyclohexanol (25 mg/kg/day) orally for a period of 40 days. Group 2 rabbits were allowed to recover for a period of 70 days after cessation of cyclohexanol treatment. Twenty-four hours after the administration of the final dose the testes and epididymides were removed. In group 3 the administration of cyclohexanol did not cause loss of bodyweight. A significant ($P<0.01$) reduction was noticed in the weights of testes and epididymides. Adrenal weights were not changed. Microscopic examination of the testes revealed loss of type A spermatogonia, spermatocytes, spermatids and spermatozoa. The nuclei of the Leydig cells were reduced in diameter ($P<0.01$). In the epididymides the luminal epithelium was reduced and the stereocilia were scanty. Total RNA, protein, sialic acid and glycogen contents were reduced ($P<0.01$) in the testes and epididymides. The testicular cholesterol was increased ($P<0.01$), and the acid phosphatase enzyme activity was decreased. Haematological data of treated rabbits were within normal range. After the recovery phase (group 2) normal spermatogenesis was seen. The organ weights, seminiferous tubules and Leydig cells nucleus dimensions were restored to normal. The biochemical changes observed returned to subnormal values during a 70 day period after cessation of cyclohexanol treatment.

4.5.3 Risks of exposure of male animals with respect to gestation of the partner, and the offspring

No data available.

4.5.4 Risks of exposure of both male and female animals (mating partners) with respect to gestation and the offspring

No data available.

4.5.5 Conclusion animal data

With respect to risk on fertility after exposure of males (4.5.2) it can be concluded that cyclohexanol causes testicular atrophy and induces an subfertility state by inhibiting the process of spermatogenesis at the spermatocyte and spermatid levels. It can be concluded that the NAEL will be lower than 15 mg/kg/day (s.c. injection) and 25 mg/kg/day (orally). These values are far below the present MAC (200 mg/m^3). There are no data available of effects after exposure by inhalation. Sufficient data are lacking to set a well documented NAEL with respect to risks to reproductive organs, endocrine system, fertility, gestation, prenatal development and the offspring after exposure of female and/or male animals.

4.6 METHANOL ISN 20661

4.6.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

No data available.

4.6.2 Risks of exposure of female animals with respect to gestation and prenatal development

Nelson et al. (1985) exposed groups of rats to 0, 6625 mg/m3 (5000 ppm), or 13250 mg/m3 (10000 ppm) methanol by inhalation for 7h/day on day 1-19 of pregnancy, and to 26500 mg/m3 (20000 ppm) for 7h/day on day 7-15 of pregnancy. The dams were killed on day 20 of gestation. At the highest dose level the dams showed a slightly unsteady gait after the first few days (number of days ?) of exposure. Methanol treatment had no effect on the number of corpora lutea nor on implantations or on the percentage of dead or resorbed fetuses. However, at the mid-and high dose level, methanol depressed fetal weights in a dose-related manner. Number of abnormal fetuses increased with increasing methanol concentrations, but was statistically significant ($P<0.05$) only at the high dose level. There were nine fetuses (from four litters) with external malformations (three exencephaly plus six encephalocele) in the high-dose group. The numbers of litters with one or more skeletal malformations and visceral malformations were both significantly ($P<0.05$) increased in the highest dose group. The malformations predominantly observed were extra or rudimentary cervical ribs and urinary or cardiovascular defects.

4.6.3 Risks of exposure of female animals with respect to the offspring

Infurna et al. (1986) studied the early behavioural development of rats whose mothers had been exposed to methanol during gestation, by measuring the responses of suckling (postnatal day 1) and nest-seeking (postnatal day 2). Female rats were divided into three groups (N=10), and received distilled water or 2 % methanol in the drinking water on gestational days 15-17 or 17-19. At this concentration animals consumed about equal amounts of either methanol or tap water. Several variables were recorded during gestation and throughout the preweaning period to evaluate both maternal and fetal toxicity. The amount of methanol ingested did not vary between the two methanol groups. Daily consumption of methanol averaged 2.5 g/kg/day. No maternal toxicity was apparent as measured by weight gain, gestational duration, and daily fluid intake. Litter size, birth weight and infant mortality did not differ among the three groups. Postnatal growth (recorded on postnatal days 7, 14 and 20)

and date of eye opening were unaffected. In the suckling behavior test the proportion of pups successfully attaching to nipples did not differ significantly across the two methanol groups, but in both methanol groups the mean latency to attach to nipples was significantly ($P<0.01$) increased, when compared with the controls. Of all pups that successfully reached the nest area, those exposed prenatally to methanol exhibited significantly ($P<0.01$) prolonged latencies in comparison with controls.

4.6.4 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the partner, and the offspring

No data available.

4.6.5 Risks of exposure of both male and female animals (mating partners) with respect to gestation, and the offspring

No data available.

4.6.6 Conclusion animal data

Methanol administered by inhalation at levels of 26500 mg/m3 was teratogenic to rats (one study). The malformations observed mainly consisted of extra or rudimentary cervical ribs and urinary tract or cardiovascular defects. It is concluded that the NAEL with respect to fertility and reproduction is 6625 mg/m3 (5000 ppm) (Nelson et al. 1985). Risks of methanol exposure in female animals with respect to the offspring consisted of behavioral abnormalities in rats after oral administration of 2.5 g methanol/kg/day during gestational days 15-17 or during gestational days 17-19 (Infurna et al. 1986). Both levels were well above the current MAC (260 mg/m3).

4.7 TETRACHLOROETHYLENE

4.7.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

Levin et al. (1970) studied the effect of tetrachloroethylene on the metabolism of estrone. Female rats (N=?) were pretreated (p.o) with 1.2 ml/kg tetrachloroethylene. Twenty-four hours later tritium labeled estrone was administered i.p. The treatment did not influence the uterotropic action of estrone and the concentration of tritiated estrogen in the uterus was not increased. It was concluded, that tetrachloroethylene did not alter metabolism of estrone. In this paper most of the detailed information is concerning carbon tetrachloride.

4.7.2 Risks of exposure of female animals with respect to gestation and prenatal development

Schwetz et al. (1975) exposed rats (N=17) or mice (N=17) by inhalation to 0 or 2055 mg/m3 (300 ppm) tetrachloroethylene for 7h/day on days 6-15 of pregnancy. The control group consisted of 30 animals. Exposure to 2055 mg/m3 tetrachloroethylene was associated with a slight but statistically significant reduction (4-5 %) of the mean body weights of maternal rats, but not of mice during and/or following exposure. The mean absolute weight of the liver of mice and rats was not altered by 2055 mg/m3 tetrachloroethylene. However, the mean relative weight of the liver of mice (63 mg versus 52 mg liver/g body wt in the control group) was significantly increased.

In mice exposure to tetrachloroethylene had no effect on the average number of implantation sites per litter, litter size, the incidence of fetal resorptions, fetal sex ratios, or fetal crown-rump length. However, a significant decrease in the fetal body weight (1.19 g, control value 1.30 g) was observed.

In rats, exposure to tetrachloroethylene had no effect on the average number of implantation sites per litter, litter size, fetal sex ratios or fetal body measurements, but the resorption rate was significantly increased from 4 % in controls to 9 % in the exposed group. Examination of mouse foetuses revealed delayed ossification of the skull bones ($P<0.05$), significant ($P<0.05$)

increase in the incidence of split sternebrae and subcutaneous edema. In rats, no differences in soft tissue or skeletal abnormalities between treated groups and controls could be observed.
In a (behavioral) teratology study, Nelson et al. (1979) exposed rats to 0 (N=10) or 6166 mg/m3 (900 ppm) tetrachloroethylene for 7 h/day on days7-13 (N=10) or 14-20 (N=10) of pregnancy. The dams were affected by this level, showing reduced food consumption and lower weight gain during exposure, but histopathological examination of the maternal liver and kidney in dams sacrificed on day 21 of pregnancy revealed no abnormalities (the used parameters were not mentioned). There were no significant effects on the number, proportion born alive, or birth weights of offspring.
Reichert (1983) mentioned a study carried out by Tepe et al. (1980) in which rats were exposed by inhalation to 6852 mg/m3 (1000 ppm) for 2 weeks prior to mating and during gestation. A significant reduction in fetal body weight, decreased number of implantations and a reduced number of viable offspring was found. Upon skeletal examination of the fetuses significant increase (P=?) in the total number of anomalies (type of anomalies are not mentioned) was observed.
Hardin et al. (1981) exposed rats (N=30) and rabbits (N=20) by inhalation to 0 or 3390 mg/m3 (500 ppm) tetrachloroethylene for 6 to 7 h/day, three weeks before breeding and on gestation days 1 to 19 (rats) or 1 to 24 (rabbits). There was no evidence of maternal toxicity, fetal toxicity or teratogenicity.

4.7.3 Risks of exposure of female animals with respect to the offspring

In the behavioral teratology study of Nelson et al. (1980) -see also 4.7.2- the offspring was tested for olfactory function, neuromuscular ability, exploratory and circadian activity, aversive and appetitive learning. There was evidence of impaired neuromuscular ability in the two groups (day 7-13 or day 14-20) exposed to 6166 mg/m3. When significant differences did appear, they occurred more often when the group exposed during days 14-20 of gestation was compared with its control group. Biochemical analysis of whole brain neurotransmitter levels showed no effects in newborns, but in the 21-day-old offspring there were decreases ($P<0.05$) in dopamine levels in pups exposed during day 7-13 of gestation and acetylcholine levels in pups of both groups.

The offspring of rats exposed to 685 mg/m3 (100 ppm) (this dose was not tested in the part of the study mentioned under 4.7.2) on days 14-20 of gestation did not reveal significant differences with controls on any of the above behavioural tests. There was no exposure to 685 mg/m3 on days 7-13 of gestation. It was not stated whether neurotransmitter levels were measured in this low-dose group.

4.7.4 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the partner, and the progeny

No data available.

4.7.5 Risks of exposure of both male and female animals (mating partners) with respect to gestation, and to the offspring

No data available.

4.7.6 Conclusion animal data

Sufficient data are lacking to set a well documented NAEL.
The available data suggest some embryo-/ fetotoxicity in the mouse and rat at a level that also induces some maternal hepatotoxicity in mice (2055 mg/m3). Retarded fetal development as well as teratogenic effects were observed in rats exposed to higher levels (6852 mg/m3). In addition postnatal effects were reported in rats exposed to 6166 mg/m3 but not at an exposure level of 685 mg/m3. The present MAC value (240 mg/m3) is well below this level.
It is concluded that the NAEL with respect to fertility and reproduction is lower than 2055 mg/m3 (300 ppm).

4.8 TRICHLOROETHYLENE

4.8.1 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

Administration by inhalation

Dorfmueller et al. (1979) exposed female rats (N=30) prior to mating to 0 or 9630 mg/m3 (1800 ppm) trichloroethylene for 6 h/day, 5 days a week. Pre-mating exposure to trichloroethylene during 22 days did not affect fertility.

Oral administration

Manson et al. (1984) exposed female rats by gavage to trichloroethylene in corn oil at exposure levels of 0, 10, 100 and 1000 mg/kg/day. Each group consisted of 23 animals. Animals were treated during a total period of 6 weeks, starting 2 weeks before mating, then during mating and during pregnancy. Animals were exposed for 5 days/week during the first 3 weeks and 7 days/week during pregnancy until day 21. Females were allowed to deliver, which occurred on days 22 and 23. In females receiving 1000 mg/kg one rat died during the premating period and 2 animals died during pregnancy. Animals in the high dose group gained significantly ($P<0.01$) less weight than did controls. Body weight gain in the low- and mid dose group was comparable with controls. Premating exposure to trichloroethylene for 2 weeks did not have an adverse effect on the length of the estrus cycle, nor on fertility.

4.8.2 Risks of exposure of female animals with respect to gestation and prenatal development

Administration by inhalation

Schwetz et al. (1975) exposed rats and mice to 0 (30 rats, 30 mice) or 1605 mg/m3 (300 ppm) (18 rats, 12 mice) trichloroethylene for 7 h/day on days 6-15 of pregnancy. The animals were killed on gestation days 21 (rats) and 18 (mice). Exposure to trichloroethylene was associated with a slight but statistically significant reduction (4-5 %) of the mean body weight of maternal rats but not on mice. Absolute or relative liver weights did not show any treatment-related changes. Exposure to trichloroethylene had no effect on the average number of implantation sites per litter, litter size, incidence of

fetal resorptions, fetal sex ratios or fetal body measurements (fetal body weight and fetal crown-rump length) in mice or rats. There were no indications of soft tissue or skeletal anomalies in both species.

Dorfmueller et al. (1979) exposed rats to 0 (N=30) or 9630 (N=30) mg/m3 trichloroethylene prior to mating during 22 days (see 4.8.1) and/or on days 1-20 of pregnancy (in total 4 groups of 30 animals, see table on the next page). Daily exposure periods were 6/h/day, 5 days/week in the premating period (see 4.8.1) and 6h/day, 7 days/week during pregnancy. 15 Rats per group were killed on day 21 of pregnancy, the remaining animals (15 per group) were allowed to deliver (see 4.8.3). No treatment related effects were found in the number of corpora lutea, implantation sites/litter, fetal body weights, resorbed fetuses/litters, or sex ratios. The overall incidence of skeletal anomalies, which primarily consisted of incomplete ossification of the sternum was significantly ($P<0.05$) increased when compared with controls in the group exposed during gestation only (group C). When only the frequency of "incomplete ossification of the sternum" was compared with the controls, the difference was not significant. The incidence of displaced right ovary was significantly ($P<0.05$) increased in the group exposed during gestation only (group C). The authors considered the displaced right ovary as a minor variation, regularly seen in controls. Further, in the group exposed prior to mating as well as during gestation, the incidence of skeletal and soft tissue anomalies was actually lower than in controls (see table on the next page). Moreover, mean fetal body weights were similar in the group exposed during gestation only in comparison with controls. Therefore, the authors did not consider the increased incidence in anomalies detected in the group exposed during gestation of toxicological significance.

Summary of skeletal- and soft tissue anomalies in rat foetuses after maternal trichloroethylene exposure (Dorfmueller et al. (1979)

	Groups			
	A	B	C	D
Exposure prior to mating	+	+	-	-
Exposure during pregnancy	+	-	+	-
Number examined for skeletal anomalies	50(12)a	32(8)a	43(11)a	49(12)a
Number examined for visceral anomalies	48(12)a	32(8)a	43(11)a	48(12)a
Skeletal anomalies				
Incomplete ossification of sternum	4(2)	-	8(5)	3(3)
Total	4(2)	1(1)	13(8)b,c	5(4)
Soft tissue anomalies				
Displaced right ovary	-	1(1)	8(6)b	3(2)
total	2(2)	1(1)	8(6)	4(3)

a) number of fetuses affected (number of litters affected);

b) significantly elevated over controls ($P<0.05$).

c) other anomalies: missing 26th and 27th vertebrae, short ribs, rudimentary 14th rib.

Beliles et al. (1980)-see review paper of Hardin et al. (1984)-exposed rats (N=?) and rabbits (N=?) to 0 or 2715 mg/m3 (500 ppm) trichloroethylene by inhalation for 6 to 7 h/day, three weeks prior to breeding and during gestation days 1 to 19 (rats) or 1 to 24 (rabbits). There was no evidence of maternal toxicity, or fetal toxicity among the exposed rats and rabbits. There was no statistically significant difference in the malformation rates in either species. However, four fetuses (two fetuses in two different litters) with external hydrocephaly occurred among the trichloroethylene exposed rabbits.

Haely et al. (1982) exposed rats to 0 (N=31) or 535 mg/m3 (100 ppm) (N=30) trichloroethylene for 4 h/day from day 8-21 of pregnancy. The rats were sacrificed on the 21st day of pregnancy and the ovaries, uterus, liver, lungs, heart and the fetuses were examined. In the treated groups there was a

significant (P<0.05) reduction of fetal weight and a significant increase (P<0.005) in bipartite and absent skeletal ossification centres of the sternum, suggesting delay in fetal maturation. The frequency of fetal loss in early pregnancy was not significantly greater in the group exposed to trichloroethylene. However, the number of rats in which total resorption of all fetuses occurred was greater in the study group (P<0.05). The authors suggested, that trichloroethylene may be toxic to the fetus in the early stages of pregnancy.

4.8.3 Risks of exposure of female animals with respect to the offspring

In the postnatal part of the study of Dorfmueller et al. (1979) (see 4.8.2, dose 0 or 9630 mg/m3 4 groups with different exposure regimes) body weight measurements of offspring (N=15) up to 100 days of age as well as assessements of behavioral activity in a novel environment were determined at 10, 20 and 100 days. No significant treatment related effects were observed in postnatal body weight measurements from birth to 10 days of age. However, from 20 through 100 days of age trichloroethylene exposure in groups exposed prior to mating only (group B) or both prior to mating and during pregnancy (A) was associated with a significant decrease in body weight gain of male and female offspring (P<0.05) when compared to the group exposed during pregnancy only (group C) or to controls (group D). There were no treatment related behavioral effects in offspring from birth to 100 days of age in any of the groups.
In the postnatal part of the study of Manson et al. (1984) (see 4.8.2, dose: 0, 10, 100 and 1000 mg/kg/day, 2 weeks exposure during premating, 1 week exposure during mating and 3 weeks of exposure during pregnancy) dams delivered their litters on day 22 or 23. Pups were maintained to 31 days of age and the neonatal survival was recorded. Post hoc analysis indicated that significantly (P<0.001) more pups died in litters from the high dose group than in litters of control, low dose or medium dose groups. Post hoc analysis of the interaction between dose and sex indicated that pup mortality occurred significantly more in females than in males. The authors suggest, that the decreased neonatal survival in the high dose group was most likely related to maternal toxicity (see 4.8.2) rather than to specific developmental toxicity.

There is no explanation for the difference between sexes with relation to the pup mortality.

4.8.4 Risks of exposure of male animals with respect to sexorgans, endocrine system and fertility

Land et al. (1981) exposed male mice (5 animals per group) to 0, 0.1 or 1 maximum allowable concentration (MAC=probably 150 ppm according to Zenick et al. (1984)) of trichloroethylene for 4 h/day for 5 days. The epididymal spermatozoa were examined for morphologic abnormalities 28 days after the first exposure. Trichloroethylene exposure produced 2.43 % abnormal sperm cells at the 150 ppm (=MAC) level, which was significantly ($P<0.01$) higher than control values (1.42 %).

Zenick et al. (1984) intubated 70 day-old male rats with either 0, 10, 100 or 1000 mg/kg of trichloroethylene (10 males/group) for 5 days/week for 6 weeks. During a 3-4 week post-treatment period, the males were allowed to mate on several occasions with ovariectomized hormonally-primed females. Copulatory behavior was observed and semen evaluations were conducted in week 1 and 5 as well as in post-exposure week 4.

During the experiment all groups gained weight. However, at the end of the fifth week of exposure body weight increase was significantly less ($P<0.001$) in the 1000 mg/kg group (seven percent) as compared to the other 3 groups (15-17 %). This difference persisted but was no longer statistically significant at week 10, 4 weeks post-exposure. Upon evaluation of organ weights and organ/body weights ratios it appeared, that the 100 and 1000 mg/kg treatment groups had higher liver/body weight ratios ($P<0.05$) than the controls at week 10. In addition in the 1000 mg/kg group the males showed impaired copulatory behavior during the first 4 weeks, (the parameters of copulatory behavior were number of intermissions and ejaculation latency), but by week 5, copulation behavior was normal. It was stated by the authors, that the initial alterations in copulatory behavior may be attributed to the narcotic properties of trichloroethylene. Tolerance to this pharmacological effect may explain the absence of these effects by the fifth week of exposure. No significant trichloroethylene-related effects were seen in semen plug weights or sperm count, sperm mobility or sperm morphology during any period of the

study. Plasma testosterone levels were not changed at the end of the sixth week of exposure or 4 weeks post-exposure.

REMARK: In a pilot experiment with 2000 mg/kg there was complete mating failure.

4.8.5 Risks of exposure of male animals with respect to gestation of the partner

In a dominant lethal inhalation test, Slacik-Erben (1980) exposed male mice (50 mice per dose group) in a first series to 0, 267 mg/m3 (50 ppm), or 1080 mg/m3 (202 ppm) and in a second serie to 0 or 2406 mg/m3 (450 ppm) for 24 h. After the exposure each male was mated with one untreated female every four days, for 12 successive periods. There were no significant effects on fertilization rate, and pre-or post-implantation loss at any dose level.

4.8.6 Risks of exposure of male animals with respect to the offspring

No data available.

4.8.7 Risks of exposure of both male and female animals (mating partners) with respect to gestation, and to the offspring

Westergren et al. (1984) exposed male and female mice to 815 mg/m3 (150 ppm) trichloroethylene by inhalation for 30 days (24 hours/day). The animals were then allowed to mate, while exposure was continued for 7 days. Thereafter the males were removed, and exposure of the females was continued until the first litter was born. The animals were then removed from exposure. The specific gravity of the brain (cortex) at birth and at the age of 10 days was significantly ($P<0.01$) lower in litters from exposed mice. According to the authors this result might indicate a delayed maturation. The difference decreased with time and at the age of 30 days the pups did not differ significantly from controls.

4.8.8 Conclusion animal data

No data is available to evaluate the risk of female animals with respect to the reproductive organs and endocrine system (4.8.1). With respect to fertility (4.8.1), there is no indication in rats that trichloroethylene influences fertility (inhalation study with 9630 mg/m3, 3 weeks and oral study up to 1000 mg/kg/day).
Concerning the risk to female animals with respect to gestation and prenatal development (4.8.2) available data is conflicting. Schwetz et al. (1975) did not find any adverse effects in rats or mice, exposed to 1605 mg/m3 during organogenesis (days 6-15). However, Healy et al. (1982) reported a reduction in fetal weight and an increase in resorptions in rats exposed to 535 mg/m3 (days 8-21), but not in mice. No effect on rat fetal body weight or intra-uterine mortality rate was reported by Dorfmueller et al. (1979) after exposure of 9630 mg/m3 on days 1-20 of pregnancy.
With respect to risks of females to the offspring (4.8.3) the study of Dorfmueller et al. (1979) reported effects on postnatal growth rates after pre-mating inhalation exposure and after pre-mating and gestational inhalation exposure at 9630 mg/m3, while Manson et al. (1984) reported increased neonatal death at a dose of 1000 mg/kg/day orally.
The available data suggest, that trichloroethylene at levels below those causing (limited) maternal toxicity had no adverse effects on female fertility or pregnancy outcome.
With respect to risks of exposure of males limited information is available (only three papers). There are indications that trichloroethylene (1000 mg/m3) exerts minimal direct effects on spermatogenesis.
The present MAC value of 190 mg/m3 is at a level far below those levels causing effects in animals. Further work is, however, necessary to establish a well-documented NAEL level of thrichloroethylene.

4.9 XYLENE

4.9.1 Introduction

Xylene appears in 3 isomeric forms, ortho-, meta- and para-xylene. The commercial product is a mixture of the 3 isomers, generally with m-xylene predominating, but it may also contain substantial amounts of other contaminants such as ethyl benzene. (Barlow et al. 1982). The LD50 of ortho- and paraxylene is about two third of that of metaxylene (Ungvary, pers. comm., in Hudak et al. 1978).
By giving 14C-metaxylene by gavage to mice, Nawrot et al. (1980a) have shown that placental transfer of metaxylene and/or its metabolites is possible.

4.9.2 Risks of exposure of female animals with respect to the reproductive organs, endocrine system and fertility

Ungvary et al. (1981) studied the role of maternal sex steroid production and metabolism in the embryotoxicity of para-xylene. Groups of 20 animals were exposed to either paraxylene at 3000 mg/m3 or to air on the 10th day (24 hours) as well as on the 9th and 10th day (48 hours) of gestation. Two hours after treatment the animals were anaesthetized with phenobarbital. Blood was collected from the ovary, uterus, and femoral veins and the amount of blood and its progesterone and 17b-oestradiol levels were measured. Also the weight of the fetuses was determined on the 11th day.
Paraxylene did not significantly decrease the uterine blood flow. The 24 hour exposure to paraxylene (on day 10) did not change ovarian progesterone and 17B-oestradiol secretion significantly, but after exposure for 48 hours there was a significant ($P<0.05$) decrease in the level of both hormones in the uterine and femoral veins. After exposure for 48 hours also the weight of the fetuses was considerably decreased ($p<0.01$).
The authors concluded that disturbances in the maternal hormone metabolism should be held responsible for the embryotoxic effects of paraxylene.

4.9.3 Risks of exposure of female animals with respect to gestation and prenatal development

Inhalation

In the English summary of their otherwise Russian paper Krotov et al. (1972) concluded that paraxylene is more toxic to the maternal organism than it is to the developing embryo. According to Barlow et al. (1982) in Krotov's study rats were exposed to paraxylene by inhalation. Twenty-nine rats were exposed to 115 ppm (500 mg/m3) for 24h/day from days 1-20 of pregnancy. Xylene-exposed rats revealed a significant increase in pre-implantation loss (32 % versus 11 % in controls) (N=?), and in post-implantation loss (39 % versus 5 % in controls) (N=?). It can be concluded, that in this study paraxylene induced embryotoxic effects. No details on possible teratogenicty were given.

Hudak et al. (1978) exposed 20 rats to 230 ppm (1000 mg/m3) xylene (as a mixture of 10 % orthoxylen, 50 % metaxylene, 20 % paraxylene and 20 % ethyl benzene) by inhalation for 24 h/day on day on days 9-14 of pregnancy. Twenty-eight air-exposed animals served as controls.

This xylene mixture did not cause maternal deaths and maternal weight gain was normal. There were no effects on implants/dam, live fetuses/dam, dead or resorbed fetuses/dam or fetal weight. Upon skeletal examinations, it appeared that the frequency of fused sternebrae and extra ribs was increased ($P<0.05$ for both). There was a tendency towards retarded skeletal development (including poorly ossified sternebrae, bipartite vertebral centra and shortened 13th ribs), but statistically significant differences were not observed.

Ungvary et al. (1980) exposed groups of approximately 20 rats to ortho-, meta- or paraxylene by inhalation at levels 0, 150, 1500 or 3000 mg/m3 for 24 h/day from day 7-14 of pregnancy. The dams were killed on day 21 of gestation. Results of exposure on reproduction and litter size are summarized on the next page. Exposure to metaxylene at a level of 3000 mg/m3 resulted in mortality of 4 out of 30 rats. In addition the maternal weight gain was decreased ($P<0.05$) in this group. Mortality did not occur in the other groups. The relative liver weights were increased at all dose levels of orthoxylene ($P<0.05$). The weight of the placenta was increased after orthoxylene exposure at 1500 ($P<0.05$) and 3000 mg/m3 ($P<0.001$), while metaxylene exposure was without effect. The weight of the placenta was decreased after exposure to orthoxylene at 150 mg/m3

(P<0.05) and after exposure to paraxylene in a dose-related way at all treatment levels.
Fetal body weight was decreased in the orthoxylene exposed groups at 1500 and 3000 mg/m3 (P<0.001), in the group exposed to 3000 mg/m3 metaxylene (P<0.01) and in the 3000 mg/m3 paraxylene group (P<0.001).
The incidence of skeletal retardation was increased in the group exposed to orthoxylene at 3000 mg/m3 (P<0.05) and in all groups exposed to paraxylene. The criteria for skeletal retardation were not given.
The incidence of extra ribs was higher in comparison to the controls in the meta- and paraxylene exposed groups at 3000 mg/m3 (P<0.05 and P<0.01, respectively).
The number of rats that appeared to be pregnant at autopsy was not influenced by orthoxylene exposure. However, the pregnancy rate was decreased by 31 % in the metaxylene group exposed to 3000 mg/m3 and in the paraxylene group at 3000 mg/m3 by 20-40 %. The average number of implants/pregnant rat was decreased (P<0.05) in the group exposed to metaxylene at 3000 mg/m3. Postimplantation loss was 69 % (P<0.01) after treatment with paraxylene at 3000 mg/m3.
The results from this study are also reported (in Russian) by Ungvary et al. 1979, Tatrai et al. 1979 and Hudak et al. 1980.

Summary of effects of exposure to ortho-, meta-, or paraxylene 24h/d during day 7-14 of pregnancy on reproduction and litter data in rats (Ungvary et al., 1980).

Compound	ortho-xylene			meta-xylene			para-xylene		
Exposure level (mg/m3)	150	1500	3000	150	1500	3000	150	1500	3000
N=	20	20	20	20	20	30	20	20	20
maternal mortality						Ev			
maternal weight gain						De			
Relative liver weights	In	In	In						
Mean placental weight	De	In	In				De	De	De
Mean fetal weight		De	De			De			De
Skeletal retardation			In				In	In	In
Extra ribs						In			In
implantation/dam						De			
pregnancy rate						De			De
Postimplantation loss									In

Abbreviations: In = increased; De = decreased; Ev = evident

In a reproduction study by Mirkova et al. (1983) groups of approximately 40 pregnant rats were exposed by inhalation to xylene (6 hours a day, 5 days in a week) at concentrations of 10, 50 or 500 mg/m3 during pregnancy. The control group, consisting of 46 animals, was exposed to air. A number of the animals (N=?) was killed on day 21 of pregnancy and was examined for foetal anomalies. The remainder of the animals was allowed to litter normally. A significant increase of post-implantation loss ($P<0.05$), and a significant decrease of mean foetal weight were observed in the two higher dose groups (respectively $P<0.01$ and $P<0.05$). In addition, a significant ($P<0.01$) increase in the incidence of haemorrhages in the thoracic and abdominal cavities was found in the foetuses of the 50 and 500 mg/m3 groups.
In the high dose group xylene also induced a significant (P=?) increase in the incidence of soft tissue anomalies, such as internal hydrocephalus, microphthalmia, intracerebral haematomas, dilatation of the aorta and the auricles of the heart, and haemorrhages in the liver.
Upon skeletal examination, the number of defects appeared to be significantly increased at both higher dose levels by 62 and 177 %, respectively. At the lowest dose level (10 mg/m3), the incidence of skeletal defects, particularly of the skull, was slightly increased when compared with the controls (not statistically significant). Although this study was criticized by Hood and Ottley (1985), the arguments used do not seem very strong: although the conception rate was relatively low, the observed post implantation loss and decreased foetal weights were very obvious in the 50 and 500 mg/m^3 groups. Moreover a criterion often used as an indication of maternal health is pre-implantation loss and this parameter was essentially unaffected in each of the groups.
Ungvary et al. (1985) exposed rats (N=?) to 0, 250, 1900 or 3400 mg/m3 xylene by inhalation for 24 h/day from day 7-15 of pregnancy. The compound did not induce maternal toxicity. At all three dose levels (no dose-dependent relationship) retardation of the fetal skeletal development was observed. The incidence of extra ribs, and postimplantation fetal loss were increased at the 3400 mg/m3 level.
Ungvary et al. (1985) exposed groups (N=?) of mice to ortho,- meta-, or paraxylene by inhalation at levels 0 or 500 mg/m3 for 24 h/day from day 6-15 of pregnancy. On day 18 the animals were killed. All three solvents brought

skeletal retardation in the fetuses and increased the incidence of weight retarded fetuses.

Oral administration

Nawrot et al. (1980b) -as interpreted by Marks et al. (1982) (paper of Nawrot et al. is not available)- administered pure meta-, ortho-, or paraxylene by gavage to a unknown number of mice from day 6-15 of gestation at daily dosages of 0.30, 0.75 or 1.0 g/kg. Exposure to ortho- and paraxylene revealed evidence of maternal toxicity (no details), increased (P=?) incidence of resorptions and an increased (P=?) incidence of cleft palate among the offspring at the two higher dose levels. Administration of metaxylene resulted in a statistically significant (P=?) increase in cleft palate at the 1.0 g/kg/day group, but overt maternal toxicity was not observed.

Marks et al. (1982) administered a mixture of xylene (60.2% metaxylene, 9.1 % orthoxylene, 13.6 % paraxylene, 17.0 % ethyl benzene and <0.3 % other volatile impurities) by gavage to groups of mice on day 6-15 of gestation. The dosages were 0, 0.6, 1.2, 2.4, 3.0, 3.6 and 4.8 ml/kg/day, or 520, 1030, 2060, 2580, 3100 and 4130 mg/kg/day (density 0.86 g/ml). Each dam was killed on day 18 of gestation.

At the 4130 mg/kg/ level all 15 treated dams died. At the 3100 mg/kg/ level 12 out of 38 treated dams died and a significantly ($P<0.05$) reduced weight gain of the dams was observed. Treatment with lower dosages did not significantly affect maternal weight gain, but dams treated with 2060 and 2580 mg/kg/day had significantly ($P<0.05$) higher liver weights than those in the control group. At the 2060 mg/kg level and above the average fetal weights were significantly ($p<0.05$) lower than that of control fetuses. The numbers of implants were not significantly affected at any level tested. At the 3100 mg/kg/ level the percentage of resorptions (62.3 %) was significantly higher than in the controls (11.2 %). The average number of malformed fetuses was significantly increased ($P<0.01$) at dosages higher than 2060 mg/kg/day; cleft palate was the major malformation observed. No details on other malformations were available. The authors concluded that xylene (mixed isomers with impurity ethyl benzene) is teratogenic and embryotoxic in the mouse at levels of 2060 mg/kg/day and higher, which are dosages that show maternal toxicity and approach lethal levels.

Subcutaneous administration

Teslina (1974) has given rats s.c. xylene injections at dose levels of 0.15 g/kg (1/50 LD50) or 0.4 g/kg (1/20 LD50) on days 1-10 or 1-18 of pregnancy. Signs of maternal toxicity (reduced weight gain and kidney and haematologic changes) were observed in all dose groups. In the 0.4 g/kg/ group, treated on days 1-18, 5 rats died on day 14 (N=20). In this group combined pre- and postimplantation loss totalled 68.7 % (no separate data) and there was a reduction in fetal body weight. Lower fetal body weights were also present in the 0.15 mg/kg/group treated on days 1-18 of pregnancy, but data on pre- and postimplantation loss were not reported.

After treatment on days 1-10 of pregnancy pre-implantation loss was 57.7 % and 31.6 % in the 0.4 and 0.15 g/kg group respectively.

Since the results were reported in qualitative terms only with no significance levels and without control comparisons, finding are considered of doubtful significance.

4.9.4 Risks of exposure of female animals with respect to the offspring

Mirkova et al. (1983) studied the postnatal toxicity of xylene. A total number of 160 pregnant rats was exposed to xylene by inhalation (6 hours a day, 5 days a week) at concentrations of 10, 50 or 500 mg/m3 during pregnancy. The control group consisted of 46 animals. At 50- and 500 mg/m3 an impaired development of the F1-generation was observed: mean weight of the newborns was significantly decreased on postnatal days 7 and 21 by 15 % and 12.2 % respectively in the 500 mg/m3 group and by 13 % (postnatal day 7) and 15 % (postnatal day 21) in the 50 mg/m3 group. At the two higher dose levels xylene also induced metabolic disturbances (activity of lactate dehydrogenasae, malate dehydrogenase, glutamate dehydrogenase, adenosine triphosphatase, cytochrome oxidase, glucose-6-phosphatase and succinate dehydrogenase) measured in various tissues of F1-generation rats. At the two higher levels of exposure xylene exhibited cardiotoxic effect by disturbing metabolic processes in the myocardium. Prenatal exposure of rats to 500 mg/m3 also induced disturbances in the excretory function of the liver and in behaviour of the F1-generation (reduced horizontal movements as measured in the "open field" test).

It can be concluded, that at concentrations of 50 and 500 mg/m3, xylene causes several metabolic and behavioural disturbances in postnatal development of F1-generation.
Rosen et al. (1986) exposed rats (N=25 per exposure level) to 3500 or 7000 mg/m3 paraxylene by inhalation for 6 h/day from day 7-16 of pregnancy. Dams were allowed to give birth, and litters were counted, weighed, and observed for external malformations on postnatal day 1 and 3. Dams which had not given birth by postnatal day 3 were killed and their uteri were examined for the presence of implantation sites. Central nervous system development was evaluated by acoustic startle response on postnatal day 13, 17, 21 and 63 as well as figure-8 maze activity on postnatal day 22 and 65.
Maternal weight change during the treatment period was significantly ($P<0.05$) reduced in the 7000 mg/m3 group. No effects were seen in litter size or birth weight. There were no effects of paraxylene exposure on growth rate, figure-8 maze activity or acoustic startle response.

Summary of the risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility, pregnancy, prenatal development and offspring.

Species	exposure	dose	effects	NAEL	Ref.
rat	day 10 or day 9/10 of pregnancy	3000 mg/m3 24 or 48 h., inhalation, paraxylene	decr. fet. weight, disturb. in hormone metabolism.	<3000 mg/m3 24 or 48 h	Ungvary et al. (1981)
rat	day 1-20 of pregnancy	500 mg/m3/ 24h/day inhalation paraxylene	incr. pre- and postimpl. loss	<500 mg/m3 24h/day	Krotov et al. (1972)

Summary of the risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility, pregnancy, prenatal development and offspring (continued 1).

Species	exposure	dose	effects	NAEL	Ref.
rat	day 7-16 of pregnancy	3500, 7000 mg/m3/6h/day inhalation paraxylene	red. weight of dams	<3500 mg/m3 6h/day	Rosen et al. 1986
rat	day 9-14 of pregnancy	1000 mg/m3/ 24h/day inhalation mixture	skeletal malform.	<1000 mg/m3 24h/day	Hudak et al. 1978
rat	day 7-14 of pregnancy	0, 150, 1500 3000 mg/m3/ 24h/day, inhalation paraxylene	pre- and postimpl. loss, decr. weight of placenta and fetus, skeletal retard., extra ribs.	<150 mg/m3 24h/day	Ungvary et al. (1980)
rat	day 7-14 of pregnancy	0, 150, 1500 3000 mg/m3/ 24h/day, inhalation, metaxylene	mort. and growth retard. of dams, pre- and post implant. loss, decr. weight fetus, extra ribs.	1500 mg/m3/ 24h/day	Ungvary et al. (1980)
rat	day 7-14 of pregnancy	0, 150, 1500 3000 mg/m3/ 24h/day, inhalation orthoxylene	incr. weight liver dams, decr. weight fetus, skeletal retard.	<150 mg/m3 24h/day	Ungvary et al. (1980)

Summary of the risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility, pregnancy, prenatal development and offspring (continued 2).

Species	exposure	dose	effects	NAEL	Ref.
rat	day 1-21 of pregnancy	10, 50, 500 mg/m3/6h/day inhalation mixture	post-impl. loss decr. weight fetus, skeletal malf., decr. weight F1, metabolic defects F1.	10 mg/m3/6h day	Mirkova et al. 1983
rat	day 7-15 of pregnancy	250, 1900, 3400 mg/m3/ 24h/day inhalation mixture	postimpl. loss skeletal retard., extra ribs.	<250 mg/m3/ 24h/day	Ungvary et al. 1985
mouse	day 6-15 of pregnancy	0, 500 mg/m3 24h/day, inhalation, orthoxylene	decr. weight fetus, skeletal retard.	<500 mg/m3	Ungvary et al. (1985)
mouse	day 6-15 of pregnancy	0, 500 mg/m3 24h/day inhalation metaxylene	decr. weight fetus, skeletal retard.	<500 mg/m3	Ungvary et al. (1985)
mouse	day 6-15 of pregnancy	0, 500 mg/m3 24h/day, inhalation paraxylene	decr. weight fetus, skeletal retard.	<500 mg/m3	Ungvary et al. (1985)
mouse	day 6-15 of pregnancy	0.30, 0.75, 1 g/kg/day, oral, o-xylene.	maternal tox., cleft palate.	300 mg/kg/ day	Nawrot et al. (1980b).

Summary of the risks of exposure of female animals with respect to the reproductive organs, endocrine system, fertility, pregnancy, prenatal development and offspring (continued 3).

Species	exposure	dose	effects	NAEL	Ref.
mouse	day 6-15 of pregnancy	0.30, 0.75, 1 g/kg/day oral, p-xylene.	maternal tox., cleft palate.	300 mg/kg/ day	Marks et al. (1982)
mouse	day 6-15 of pregnancy	0.30, 0.75, 1 g/kg/day oral., m-xylene	cleft palate	7500 mg/kg/ day	Marks et al. (1982)
mouse	day 6-15 of pregnancy	0, 0.5, 1.0, 2.1, 2.6, 3.1 and 4.8 g/ kg/day, oral mixture	mortal., growth retard. and incr. liver weight of dams, fet. resorpt. and fet. malformations (cleft palate)	1030 mg/kg/ day	Marks et al. (1982)
rat	day 1-10 or day 1-18 of pregnancy	0.15, 0,4/ g/kg/day, s.c. inject. mixture	maternal tox., pre- and post-implantation loss, decreased fetus weight	<0.15 g/kg	Teslina (1974)

4.9.5 Risks of exposure of male animals with respect to the reproductive organs, endocrine system, fertility, gestation of the partner, and the offspring

No data available.

4.9.6 Risks of exposure of both male and female animals (mating partners) with respect to the gestation, and the offspring

No data available.

4.9.7 Conclusion animal data

Concerning the risks of exposure of female animals with respect to gestation and prenatal development is can be concluded, that xylene is embryotoxic when administrated by inhalation. It induces pre- and postimplantation loss, reduced body weight and retarded ossification of the fetal skeleton. In addition, after oral administration xylene appears to be teratogenic in the mouse (cleft palate).
Although of the 3 isomers paraxylene appeared to be the least toxic to pregnant animals, this isomer revealed embryotoxicity at lower levels than any of the other isomers (Ungvary et al. 1979; Barlow et al. 1982).
Exposure by inhalation to 50 mg/m3 xylene was reported to induce already impaired development of the F1-generation (Mirkova et al. 1983).
There is no sufficient literature data available to draw solid conclusions about the overall NAEL for any of the isomers. Provisionally the NAEL level for orthoxylene can be set at about 300 mg/kg/day (oral administration) or less than 150 mg/m3/24h (inhalation). For metaxylene the NAEL might be set at about 7500 mg/kg/day (oral administration) or about 1500 mg/m3/24h (inhalation). For paraxylene the NAEL might be about 300 mg/kg/day (oral administration) or less than 150 mg/m3/24h (inhalation).
For a mixture of xylene isomers the NAEL appeared to be about 0.15 g/kg (s.c. injection, of doubtful significance, due to deficient reporting), or 1030 mg/kg/day (oral administration) or about 10 mg/m3/6h/day (inhalation). Since there is not sufficient data available to draw overall conclusion on NAEL's for each of the isomers or the mixture and, moreover, in practice exposure to xylene at the workplace will mostly be to mixtures of unknown composition, it seems appropriate to set the NAEL's for xylene at the lowest reliable values observed in the literature: 300 mg/kg/day by the oral route, and 10 mg/m3/day by inhalation. These values are below the present MAC (435 mg/m3). Therefore

there is urgent need for further research. Reconsideration of the present MAC is recommended.

5. SUMMARIZING CONCLUSIONS ON HUMAN AND ANIMAL DATA

Although the available animal studies are hardly suitable neither quantitatively nor qualitatively for the assessment of human risk with respect to fertility and reproduction, the following remarks can be made:

1. Upon the evaluation of the human data with respect to women exposed to solvents, it was concluded that the data are inadequate to prove an increased risk of infertility. Also the occurrence of endocrinological effects after exposure to solvents could not be established. Concerning the risk of exposure of female animals with respect to the endocrine system and fertility seven studies are available. One study with paraxylene, as well as three studies with carbon tetrachloride showed effects on the endocrine system, whereas a limited study with tetrachloroethylene did not show such effects. The results of two studies with trichloroethylene indicated that trichloroethylene does not influence fertility. However, the available animal data are not sufficient to draw any conclusion with respect to a possible increased risk of disturbances in the endocrine system, or fertility after exposure of female animals to solvents.
2. The available animal data on xylene, carbon tetrachloride, trichloroethylene, tetrachloroethylene, and the few data on 2-butanone, methanol, and acetone all indicate that exposure to solvents during pregnancy may induce pre- and postimplantation loss, may further result in retarded fetal development and may even induce teratogenic effects. The results from animals studies are quite well in agreement with the human data on spontaneous abortion and congenital malformations.
3. The overall evidence from human data that solvents are excreted in breast milk can be considered sufficient. However, no reliable data exist on potential health risks for the suckling infant. Follow-up studies of infants are needed. Unfortunately no animal data are available on this subject.

4. Since only a few studies were reported on effects of male exposure on fertility and reproduction, the risks of exposure of male animals with respect to reproductive organs, endocrine system, fertility, gestation of the partner and effects on the offspring could not be evaluated.
5. Workers usually are not exposed to a single solvent, but to mixtures of a unknown composition. The solvents most frequently mentioned in the literature on human data are xylene, acetone, butyl acetate (no animal data available), methanol, ethylacetate (no animal data available) and butanol.

From this literature survey it appeared that there is a considerable lack of information with respect to effects of these solvents both on human and laboratory animal fertility and reproduction: of the above mentioned solvents only xylene is reasonably studied in animals.
Since human exposures to a number of organic solvents is widespread and there are at least indications from both human and animal data that exposure may induce prenatal morality (abortion) and developmental disorders, it is recommended that additional animal studies should be conducted with a number of widely used solvents. Further, effects of exposure to a combination of solvents on fertility and reproduction of laboratory animals should also be studied.

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Table 1a - Gynaecological disorders in women occupationally exposed to solvents (adopted from Zielhuis et al, 1984)

Author, year of publication, country	Exposed group, type of exposure (E)	Control group (C)	Reported effects	Comments
Helmer (1944) Sweden	n=169 women, 15 men, exposed to benzene; very high exposure	-	In 58 of 169 women chronic benzene-poisoning, with increased propensity for bleeding	Quoted by NIOSH (1974); very high exposure
Michon (1965) Poland	n=500; age 20-40 yr; exposed to benzene, toluene *, xylene probably below 5.50 and 50 mg/m^3 respectively; shoe production	n=100	Greater prevalence of disturbed menstruation, particularly profuse and/or extended bleeding; no increased irregularity	Quoted from summary; limited data; no classification according to age and obstetric history; possible effect of work posture (standing)
Postolache (1975), Japan	n=about 100; exposed to acetone, butyl-acetate, toluene * up to probably respectively 200, 200 and 50 mg/m^3	-	Greater prevalence of disturbed menstruation	Quoted from summary; limited data
Matsushita et al (1975),	n=38; age 20,7±5.2 yr; toluene * up to 375 mg/m^3, 3 yrs	n=16	Painful menstruation in 19 of 38 (E) and in 3 of 16 (C)	Sometimes also exposed to benzin *
Syrovadko (1977), USSR	n=140; exposed to toluene * up to 420 mg/m^3, 4-20 yrs	n=201	Up to five times greater prevalence of disturbed menstruation. Prolapse of uterus 6.5 % (E) 0.5 % (C) ($p<0.05$)	Quoted by WHO (1981); limited data; prolapse may be due to working posture
Izmerow et al (1978), USSR	Exposure to benzin * in rubber (tire) production) n=63; exposure to dimethyl-dioxane (20-25 mg/m) and formaldehyde (1-2 mg/m^3)	-	No change in vaginal cells, indicating absence of disturbed function of ovary. In women exposed for >4 yrs disturbed menstruation in 31.7 % (E), 6.6 % (C) ($p<0.005$); increased frequency in 17.4 % (E), 1.1 % (C) irregularity and profuse bleeding in 11.1 % (E), 2.2 % (C)	Review of eastern European literature; limited data

* The presence of a high percentages of benzene cannot be excluded

Table 1b - Other studies on gynaecological disorders

Author, year of publication, country	Exposed group, type of exposure (E)	Control group (C)	Reported effects	Comments
Syrovadko and Malysheva (1977), USSR	n=311, enamellers exposed to chlorobenzene (av. 72.3 mg/m^3), tricresol (av. 4.3 mg/C^3), ethylene glycolmonomethylether and solvent naphtha (both) reported to be low)	administrative silica plant workers (n?), hospital workers (n?)	prevalence of gynaecological disorders particularly inflammatory processes, benign neoplasms, cervical disorders, in E prevalence increased, but not in comparison to administrative workers, but 2.9 to 9.4 times higher than in both other control groups	Combined exposure also to solvent chemicals; lack of detailed data on methods and design
Sirokov (1976), USSR	n=378 workers involved in the production of ethylene diamine, dichloroethane, dichloroethane, vinylchloride, PVC; within this group 208 exposed to chlorinated HC's, 55 exposed to amines and chlorinated HC's. The concentration in workroom air exceeded the USSR-MPC in the case of ammonia, acetylene, Cl, and dust	n=155, not or less exposed n=135, working in a tool production plant	cervicitis: E (%) 16.8, C (%) 9.6, P <0.05 adnexitis: E (%) 12.1, C (%) 5.2, P <0.05 colpitis: E (%) 12.4, C (%) 5.2, P <0.05 genital infantilism: E (%) 6.1, C (%) 5.7, P <0.05	unfavourable climatic cond. (up to 37 °C); also exposure non-solvent chemicals; lack detailed data on methods and design
Mikhailova et al (1971) USSR	age av. 37 yr; av. duration of exposure 9 yr	E + C, n=260	in those exposed to benzene (n?) 18.5 % menstrual disorders; in shop workers (C) 10.5 %; in C-groups exposed to other chemicals were 18.5 %; also other gynaecological disorders increased in E	lack of essential details methods and design
Mukhamatova and Vozovaja (1972)	female gluing operatives (n=369, 20-40 yrs of age, duration of exposure 40 %>6 yr) exposed to petroleum (containing benzene?), chlorinated hydrocarbons, particularly dichloroethane and methylene chloride; levels in 41.5 % of samples 1.2-2.4 times higher than the USSR-MPC	controls (n=660) with similar age	E: gynaecological disorders, 54.2 % including menstrual disorders (26.1 %); in E 3 times more polymenorrhoea than in C	lack of essential details on methods and design

Table 2a - Studies from before 1980 on spontaneous abortion in female workers exposed to solvents

author year of publication, country	number of subjects exposed (E)	type and intensity of exposure	number of controls (C)	results	comments
Ragucci (1969), Italy	15 cases	benzene poisoning	no C	abortions in 7 of 15 pregnancies	quoted by Schardein (1985)
Mikhailova et al (1971), USSR	see table 1b	benzene and homologues	see table 1b	in E 4.5 % spontaneous abortions, in C-group 2.1 to 14.1 %	incidence in some groups far below expectation; lack of details on methods and design
Mukhamatova and Vozovaja (1972), USSR	see table 1b 250 pregnant gluers	see table 1b	see table 1b controls	in E and C many induced abortions; in E 17.2 % spontaneous abortions, in C 4.9 %	incidence C is far below expectation; lack of essential details on methods and design
Postalche (1974), Poland	about 100	acetate, butyl-acetate, toluene, probably below 200, 200 and 50 mg/m^3 respectively	?	increased risk, no quantitative data	quoted by Zielhuis et al (1984) 94 % of female workers showed no specific signs of toxicity
Syrovadko (1977), USSR	140	toluene 25-140 mg/m^3	210	no increased risk	quoted by Zielhuis et al (1984) in 28 % of E autonomic vascular dysfunction; in C 15 % ($p<0.05$)

Table 2b - Studies from 1982 onwards on spontaneous abortion in female workers exposed to solvents

author, year of study, country	results of subjects exposed	type and intensity of exposure	number of controls	results
Elsyneva (1982), USSR	unknown	exposure to acetone, 200 up to 600 mg/m^3; fiber production and textile department	unknown	impending abortion, $p<0.001$; for other gynaecologicial disorders also significantly increased percentage; increasing prevalence with longer duration of exposure
Hemminki et al (1984), Finland	nation-wide	laundry, exposure to tetrachloroethene	nation-wide	no increased risk
Heidam (1984a), Denmark	1431 factory workers, 81 painters	various solvents and other chemicals	1034 non-exposed workers	no increased risk
Heidam (1984b), Denmark	881 laboratory workers	various solvents and other chemicals	1971 less exposed controls	no increased risk
Axelsson et al (1984), Sweden	a group of workers with 556 who had been pregnant; comparison between those exposed during the first trimester of pregnancy and those before or after pregnancy			
Lindbohm et al (9184), Finland	nation-wide	various occupational group	nation-wide	no increased risk in those exposed to solvents. Only in laundry workers significantly increased risk
McDonald and McDonald (1986)	about 400	leather factory, exposure to unspecified solvents in glues and paints	nation-wide	no increased risk
Taskinen et al (1986), Finland	nation-wide 1795 pregnancies	pharmaceutical industries, exposure to several solvents	comparison between exposure and before/after pregnancy	overall no increased incidence case-control study; increased risk when exposed during pregnancy to methylenechloride; indication of an exposure-response relationship with regard to number of solvents exposed to

Table 3 - Causal epidemiologic evidence of reproductive risks in exposure to organic solvents below or around the present MAC's

reproductive organic endpoint	n	high level evidence	limited evidence	low level evidence	inadequate evidence
Risk of exposure of females with respect to:					
- menstrual disorders	10		↑		
- other gynaecological disorders				↑	
- effects on the endocrine system	2				X
- fertility	3				X
- cancer of reproductive organs and breast	3				X
- spontaneous abortion	13			↑	
- congenital malformations	11				
- CNS				↑	
- orofacial cleft			↑		
- gastrointestinal tract					X
- birth weight/length prematurity	7				X
- stillbirth, perinatal mortality	5			↑	
- offspring (through lactation)	2				X
Risk of exposure of males with respect to:					
- reproductive organs, endocrine system	6				X
- fertility			=		
- spontaneous abortion	3				X
- congenital malformations	2				X
- birth weight/length	1				X

legenda
↑ increased
= not affected
X inadequate evidence
n number of epidemiologic studies reviewed